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(12) **United States Patent**
McIver et al.(10) **Patent No.:** **US 6,300,341 B1**
(45) **Date of Patent:** **Oct. 9, 2001**(54) **2-SUBSTITUTED HETEROCYCLIC
SULFONAMIDES**

5,859,031 1/1999 Hamilton et al. 514/343

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Cincinnati, OH (US)(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) **Appl. No.:** **09/400,679**(22) **Filed:** **Sep. 21, 1999****Related U.S. Application Data**(60) Provisional application No. 60/102,539, filed on Sep. 30,
1998.(51) **Int. Cl.**⁷ **A61K 31/47; A61K 31/40;**
C07D 216/26; C07D 215/58; C07D 209/42(52) **U.S. Cl.** **514/309; 514/303; 514/312;**
514/416; 514/419; 546/141; 546/153; 546/156;
546/118; 548/482; 548/491(58) **Field of Search** **514/416, 419,**
514/309, 312, 303; 546/141, 153, 156,
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Primary Examiner—Bernard Dentz(74) **Attorney, Agent, or Firm**—Kelly McDow-Dunham;
Catherine U. Brown; Steven W. Miller(57) **ABSTRACT**

The present disclosure describes novel compounds and
 compositions which are particularly useful for treating hair
 loss in mammals, including arresting and/or reversing hair
 loss and promoting hair growth. The present compounds and
 compositions may also be useful against a variety of disor-
 ders including, for example, multi-drug resistance, human
 immunodeficiency virus (HIV), cardiac injury, and neuro-
 logical disorders, and may be useful for controlling parasites
 and invoking immunosuppression.

19 Claims, No Drawings

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2-SUBSTITUTED HETEROCYCLIC
SULFONAMIDES

CROSS REFERENCE

This application claims priority under Title 35, United States Code § 119(e) from Provisional Application Ser. No. 60/102,539, filed Sep. 30, 1998.

FIELD OF THE INVENTION

The present invention relates to novel compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The present compounds and compositions may also be useful against a variety of disorders including, for example, multi-drug resistance, human immunodeficiency virus (HIV), cardiac injury, and neurological disorders, and may be useful for controlling parasites and invoking immunosuppression.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair regrowth which causes partial or full baldness. Such baldness is cosmetically unappealing, and is particularly distressing to the person experiencing the hair loss.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth is ceased. The next phase, telogen, is often characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. This cycle is repeated throughout hair growth. Wherein hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

There have been many attempts in the literature to invoke the regrowth of hair by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as Rogaine® by Pharmacia & Upjohn), and oral finasteride (marketed as Propecia® by Merck & Co., Inc.).

There are conflicting reports, however, regarding the ability of minoxidil to grow hair. In fact, early clinical studies investigating decreased blood pressure via the use of minoxidil did not even mention hypertrichosis (hair growth)

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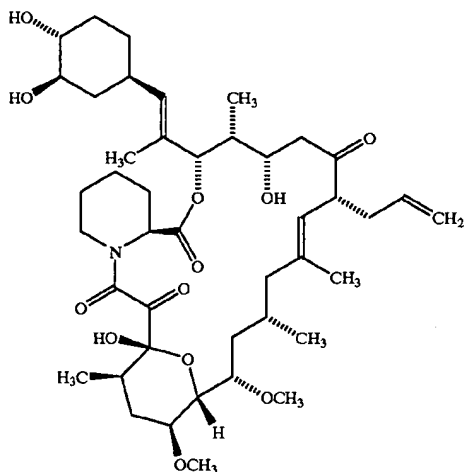
as a side effect. See Dormois et al., "Minoxidil in Severe Hypertension: Value When Conventional Drugs Have Failed", *American Heart Journal*, Vol. 90, pp. 360-368 (1975). Indeed, the manufacturers of minoxidil have reported only limited hair growth in a portion of patients using minoxidil. See eg., *Physician's Desk Reference*®, 49th Ed. (1995), p. 2580. Furthermore, serious side effects of minoxidil are possible, including vasodilation (which leads to retention of fluid around the heart and increased heart rate), difficulty in breathing, and weight gain. *Physician's Desk Reference*®, 49th Ed. (1995), p. 2581.

Furthermore, while early indicators show that Propecia® may be more effective than Rogaine®, patients using Propecia® are experiencing limited hair growth. See *The New England Journal of Medicine*, Vol. 338, No. 9, Feb. 26, 1998. Furthermore, potential side effects of Propecia® are serious. Propecia® may cause impotence, decreased sexual drive, decreased volume of ejaculate, breast tenderness and enlargement, and hypersensitivity reactions, including lip swelling and skin rash. Furthermore, Propecia® is not indicated for women and children. In fact, women who are pregnant or potentially pregnant should not even handle crushed or broken tablets containing the drug. See *Physician's Desk Reference*®, 52th Ed. (1998), p. 1737 and *The New England Journal of Medicine*, Vol. 338, No. 9, Feb. 26, 1998.

Interestingly, the immunosuppressive agents cyclosporin A and FK506 are known to invoke a prominent hypertrichotic side effect. See Iwabuchi et al., "Effects of Immunosuppressive Peptidyl-Prolyl cis-trans Isomerase (PPIase) Inhibitors, Cyclosporin A, FK506, Ascomycin, and Rapamycin, on Hair Growth Initiation in Mouse: Immunosuppression is not Required for New Hair Growth", *Journal of Dermatological Science*, Vol. 9, pp. 64-69 (1995); Yamamoto et al., "Hair Growth-Stimulating Effects of Cyclosporin A and FK506, Potent Immunosuppressants", *Journal of Dermatological Science*, Vol. 7 (suppl.), pp. S47-S54 (1994); Yamamoto et al., "Stimulation of Hair Growth by Topical Application of FK506, a Potent Immunosuppressive Agent", *Journal of Investigational Dermatology*, Vol. 102, pp. 160-164 (1994); Jiang et al., "Induction of Anagen in Telogen Mouse Skin by Topical Application of FK506, a Potent Immunosuppressant", *Journal of Investigational Dermatology*, Vol. 104, pp. 523-525 (1995); McElwee et al., "Topical FK506: A Potent Immunotherapy for Alopecia Areata? Studies Using the Dundee Experimental Bald Rat Model", *British Journal of Dermatology*, Vol. 137, pp. 491-497 (1997); Maurer et al., "Hair Growth Modulation by Topical Immunophilin Ligands", *American Journal of Pathology*, Vol. 150, No. 4, pp. 1433-1441 (1997); and Paus et al., "Hair Growth Control by Immunosuppression", *Arch. Dermatol. Res.*, Vol. 288, pp. 408-410 (1996). However, use of these compounds as hair growth actives may not be desirable due to their striking potency as immunosuppressive agents.

FK506 is a complex, macrocyclic molecule having the following structure:

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Stocks et al., "The Contribution to Binding of the Pyranoside Substituents in the Excised Binding Domain of FK-506", *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 12, pp. 1457-1460 (1994). Analogs closely resembling this complex macrocycle have been disclosed as having hair growth properties in the form of, for example, alopecia areata and/or male pattern baldness. See, e.g., Kawai et al., U.S. Pat. No. 5,541,193, assigned to Abbott Laboratories, issued Jul. 30, 1996; Asakura et al., U.S. Pat. No. 5,496,564, assigned to Fujisawa Pharmaceutical Co., issued Mar. 5, 1996; Baumann et al., U.S. Pat. No. 5,352,671 assigned to Sandoz Ltd., issued Oct. 4, 1994; and Rupprecht et al., U.S. Pat. No. 5,550,233, assigned to Merck & Co., Inc., issued Aug. 27, 1996.

However, excitement related to the hypertrichotic activities of cyclosporin A and FK506 is somewhat quelled by the lack of reports of hypertrichosis by various smaller, non-macrocyclic immunosuppressive and non-immunosuppressive compounds which are less complex in structure than FK506. See Steiner et al., WO 96/40140, assigned to Guilford Pharmaceuticals, Inc., published Dec. 19, 1996; Hamilton et al., WO 96/40633, assigned to Guilford Pharmaceuticals, Inc., published Dec. 19, 1996; Steiner et al., U.S. Pat. No. 5,696,135, assigned to GPI NIL Holdings, Inc., issued Dec. 9, 1997; Hamilton et al., U.S. Pat. No. 5,614,547, assigned to Guilford Pharmaceuticals, Inc., issued Mar. 25, 1997; Steiner et al., WO 97/16190, assigned to Guilford Pharmaceuticals, Inc., published May 9, 1997; Zelle et al., WO 96/36630, assigned to Vertex Pharmaceuticals, Inc., published Nov. 21, 1996; Armistead et al., WO 97/36869, assigned to Vertex Pharmaceuticals, Inc., published Oct. 9, 1997; Zelle et al., WO 96/15101, assigned to Vertex Pharmaceuticals, Inc., published May 23, 1996; Armistead et al., WO 92/19593, assigned to Vertex Pharmaceuticals, Inc., published Nov. 12, 1992; Armistead et al., WO 94/07858, assigned to Vertex Pharmaceuticals, Inc., published Apr. 14, 1994; Zelle et al., WO 95/26337, assigned to Vertex Pharmaceuticals, Inc., published Oct. 5, 1995; Duffy et al., WO 92/21313, assigned to Vertex Pharmaceuticals, Inc., published Dec. 10, 1992; Armistead et al., U.S. Pat. No. 5,192,773, assigned to Vertex Pharmaceuticals, Inc., issued Mar. 9, 1993; Armistead et al., U.S. Pat. No. 5,330,993, assigned to Vertex Pharmaceuticals, Inc., issued Jul. 19, 1994; Armistead et al., U.S. Pat. No. 5,622,970, assigned to Vertex Pharmaceuticals, Inc., issued Apr. 22, 1997; Armistead et al.,

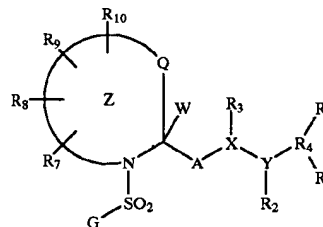
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U.S. Pat. No. 5,654,332, assigned to Vertex Pharmaceuticals, Inc., issued Aug. 5, 1997; Armistead et al., U.S. Pat. No. 5,620,971, assigned to Vertex Pharmaceuticals, Inc., issued Apr. 15, 1997; Zelle et al., U.S. Pat. No. 5,543,423, assigned to Vertex Pharmaceuticals, Inc., issued Aug. 6, 1996; Armistead et al., U.S. Pat. No. 5,516,797, assigned to Vertex Pharmaceuticals, Inc., issued May 14, 1996; Armistead et al., U.S. Pat. No. 5,665,774, assigned to Vertex Pharmaceuticals, Inc., issued Sep. 9, 1997; Andres et al., "Conformationally Defined Analogs of Prolylamides. trans-Prolyl Peptidomimetics", *Journal of Organic Chemistry*, Vol. 58, pp. 6609-6613 (1993); and Armistead et al., "Design, Synthesis and Structure of Non-macrocyclic Inhibitors of FKBP12, the Major Binding Protein for the Immunosuppressant FK506", *Acta Crystallographica*, D51, pp. 522-528 (1995).

Surprisingly, the present inventors have discovered a novel class of compounds which arrest and/or reverse hair loss or promote hair growth but do not share the complex, macrocyclic structure of FK506. The present inventors have further discovered compounds among this novel class which invoke hair growth yet are surprisingly non-immunosuppressive or are nominally immunosuppressive. The minimized and/or absent immunosuppressive activity of these hypertrichotic compounds are distinct advantages as compared to the immunosuppressive compounds cyclosporin A and FK506.

SUMMARY OF THE INVENTION

The present invention relates to compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The present compounds and compositions may also be useful against a variety of disorders including, for example, multi-drug resistance, human immunodeficiency virus (HIV), cardiac injury, and neurological disorders, and are useful for controlling parasites and invoking immunosuppression. The compounds of the present invention have the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein the moieties Z, Q, W, X, Y, V, A, G, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ are defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth.

In addition to discovering that the present compounds are useful for treating hair loss, the present inventors have also surprisingly discovered that immunosuppression is not required for hair growth stimulation. The present inventors

have further discovered compounds that are useful for treating hair loss but are surprisingly non-immunosuppressive. Preferred compounds of the present invention are therefore, as defined herein, non-immunosuppressive. The present compounds are also useful for treating a variety of other conditions as described herein below.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein "salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). Such acceptable salts must, when administered, be appropriate for mammalian use.

As used herein unless otherwise specified, "alkenyl" is an unsubstituted or substituted, straight or branched hydrocarbon chain radical having from 2 to about 15 carbon atoms; preferably from 2 to about 10 carbon atoms; more preferably from 2 to about 8 carbon atoms, and most preferably from about 2 to about 6 carbon atoms. Alkenyls have at least one olefinic double bond. Non-limiting examples of alkenyls include vinyl, allyl, and butenyl.

As used herein unless otherwise specified, "alkoxy" is an oxygen radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Examples of alkoxy radicals include —O-alkyl and —O-alkenyl. An alkoxy radical may be substituted or unsubstituted.

As used herein unless otherwise specified, "aryloxy" is an oxygen radical having an aryl substituent. An aryloxy radical may be substituted or unsubstituted.

As used herein unless otherwise specified, "alkyl" is an unsubstituted or substituted, straight or branched saturated hydrocarbon chain radical having from 1 to about 15 carbon atoms; preferably from 1 to about 10 carbon atoms; more preferably from 1 to about 6 carbon atoms; and most preferably from 1 to about 4 carbon atoms. Preferred alkyls include, for example, methyl, ethyl, propyl, iso-propyl, and butyl.

As used herein, "alkylene" refers to an alkyl, alkenyl, or alkynyl which is a diradical. For example, "methylene" is —CH₂—. Alkylenes may be substituted or unsubstituted.

As used herein unless otherwise specified, "aryl" is an aromatic ring radical which is either carbocyclic or heterocyclic. Preferred aryl groups include, for example, phenyl, benzyl, tolyl, xylyl, cumenyl, naphthyl, biphenyl, thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, triazolyl, tetrazolyl, benzothiazolyl, benzofuryl, indolyl, indenyl, azulenyl, fluorenyl, anthracenyl, oxazolyl, isoxazolyl, isotriazolyl, imidazolyl, pyrazolyl, oxadiazolyl, indoliziny, indolyl, isindolyl, purinyl, quinoliziny, quinolinyl, isoquinolinyl, cinnoliny, and the like. Aryls may be substituted or unsubstituted.

As used herein unless otherwise specified, "arylalkenyl" is an alkenyl radical substituted with an aryl group or an aryl

radical substituted with an alkenyl group. Arylalkenyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "arylalkyl" is an alkyl radical substituted with an aryl group or an aryl radical substituted with an alkyl group. Preferred arylalkyl groups include benzyl, phenylethyl, and phenylpropyl. Arylalkyls may be substituted or unsubstituted.

As used herein, "biohydrolyzable amides" are amides of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted in vivo by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted in vivo by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable imides" are imides of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted in vivo by a mammalian subject to yield an active compound.

As used herein unless otherwise specified, "carbocyclic ring", "carbocycle", or the like is a hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocyclic rings contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Carbocyclic rings (carbocycles) may be substituted or unsubstituted.

As used herein unless otherwise specified, "cycloalkyl" is a saturated carbocyclic or heterocyclic ring radical. Preferred cycloalkyl groups include, for example, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "halo", "halogen", "halide", or the like means a chloro, bromo, fluoro, or iodo atom radical, preferably bromo, chloro, or fluoro, more preferably chloro or fluoro.

As used herein unless otherwise specified, "heteroalkenyl" is an alkenyl radical containing carbon atoms and one or more heteroatoms within the alkenyl chain (e.g., —CHOCH₂ rather than pendant from like, e.g., C(O)) wherein the heteroatoms are selected from oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroalkenyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "heteroalkyl" is an alkyl radical containing carbon atoms and one or more heteroatoms within the alkyl chain (e.g., —CH₂OCH₂ rather than pendant from like, e.g., C(O)) wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroalkyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "heteroaryl" is an aryl radical containing carbon atoms and one or more heteroatoms within the aryl ring (e.g., —CHOCH—) rather than pendant from like, e.g., C(O)) wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroaryls may be substituted or unsubstituted.

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As used herein unless otherwise specified, "heteroarylalkenyl" is an arylalkenyl radical wherein the aryl group is a heteroaryl and/or the alkenyl group is a heteroalkenyl. Heteroarylalkenyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "heteroarylalkyl" is an arylalkyl radical wherein the aryl group is a heteroaryl and/or the alkyl group is a heteroalkyl. Heteroarylalkyls may be substituted or unsubstituted.

As used herein unless otherwise specified, "heterocyclic ring", "heterocycle", or the like is a ring radical comprised of carbon atoms and one or more heteroatoms in the ring wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heterocycles are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocycles contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycycles contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Heterocyclic rings (heterocycles) may be substituted or unsubstituted.

As used herein unless otherwise specified, "heterocycloalkyl" is a saturated heterocycle. Heterocycloalkyls may be substituted or unsubstituted.

As used herein unless otherwise specified, a "lower" moiety (e.g., "lower" alkyl) is moiety having 1 to about 6, preferably 1 to about 4, carbon atoms.

As used herein, "pharmaceutically acceptable" means suitable for use in a human or other mammal.

As used herein, "safe and effective amount of a compound" (or composition, or the like) means an amount that is effective to exhibit biological activity, preferably wherein the biological activity is arresting and/or reversing hair loss or promoting hair growth, at the site(s) of activity in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention.

As used herein, a "spiro moiety" is a cyclic moiety sharing a carbon on another ring, preferably the Z ring. Such spiro moiety may be carbocyclic or heterocyclic. Spiro moieties may be substituted or unsubstituted.

As used herein unless otherwise specified, the term "substituted" in reference to a group, moiety, or the like, means having one or more substituent groups each independently selected from hydrogen, alkoxy, hydroxy, nitro, amino, alkylamino, cyano, halo, carboxy, thiol, imino, and aryloxy (with additional allowed substituents on the G moiety which are selected from oxo, amido, —O-alkyl-C(O)OR₃₂, and —O-alkyl-C(O)NHR₃₂, wherein R₃₂ is selected from hydrogen and alkyl) preferably hydrogen, alkoxy, aryloxy, hydroxy, nitro, amino, halo, and thiol, more preferably hydrogen, alkoxy, hydroxy, nitro, amino, alkylamino, and halo, even more preferably hydrogen, halo, hydroxy, and alkoxy, and most preferably hydrogen.

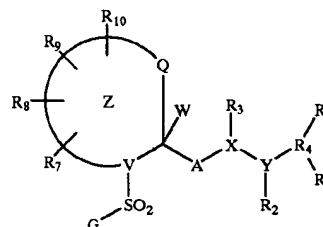
As used herein unless otherwise specified, the term "unsubstituted" means substitution by a hydrogen moiety. However, a group may alternatively be consistently described as being "substituted" wherein the substitution is with a hydrogen moiety.

As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence.

Compounds of the Present Invention

The compounds of the present invention have the structure:

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and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

- (a) V is a heteroatom wherein the heteroatom is nitrogen;
- (b) G is selected from alkyl having at least 3 carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl;
- (c) Z is a saturated or unsaturated 4-, 5-, 6-, 7-, 8-, or 9-membered heterocycle optionally containing one or more additional heteroatoms selected from O, N, S, S(O), S(O)₂, and P((O)K);
- (d) K is selected from hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl;
- (e) W is selected from nil, hydrogen and lower alkyl;
- (f) A is selected from nil and alkyl;
- (g) X and Y are each, independently, selected from C(O), N, O, and S, wherein:
 - (i) when X is C(O) then R₃ is nil and Y is selected from N, O, and S;
 - (ii) when X is N then R₃ is selected from hydrogen, alkyl, and arylalkyl, Y is C(O), and R₂ is nil;
 - (iii) when X is O then R₃ is nil, Y is C(O), and R₂ is nil; and
 - (iv) when X is S then R₃ is nil, Y is C(O), and R₂ is nil;
- (h) R₂ and R₃ are each, independently, selected from nil, hydrogen, alkyl, and arylalkyl;
- (i) R₄ is alkyl;
- (j) R₅ and R₆ are each, independently, selected from nil, hydrogen, alkyl having at least three carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; or wherein R₅ and R₆ are bonded together to form a carbocyclic or heterocyclic ring; wherein at least one of R₅ or R₆ is not nil or hydrogen;
- (k) Q is selected from CH₂, CHR₇, NR₇, S, S(O), and S(O)₂;
- (l) R₇, R₈, and R₉, and R₁₀ are each, independently, selected from nil, hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, halo, cyano, hydroxy, oxo, imino, —R₁₄SR₁₅, —R₁₄S(O₂)R₁₅, —R₁₄S(O)R₁₅, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄C(O)OR₁₅, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, —R₁₄P(O)NR₁₅R₁₆, —R₁₄P(O)OR₁₅R₁₆, and a spiro moiety, and wherein R₇ and R₈ may be optionally bonded together to form an aromatic or saturated, carbocyclic or heterocyclic ring wherein the ring is fused to Z; wherein when A is nil and X is C(O) at least one of R₇, R₈, R₉, and R₁₀ is not nil or hydrogen;

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(m) R_{14} , and R_{15} are each, independently, selected from nil, hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; and

(n) R_{16} is selected from hydrogen and alkyl.

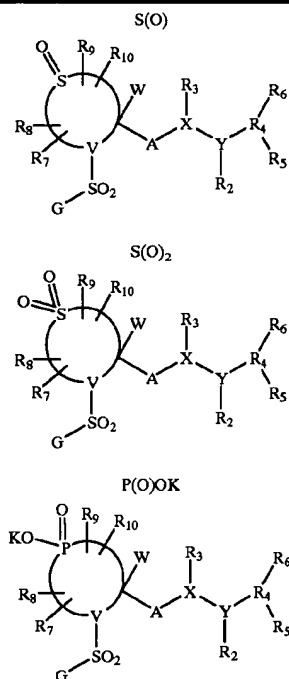
The Ring System Z

The present compounds are comprised of a ring system, Z, which is a saturated or unsaturated 4-, 5-, 6-, 7-, 8-, or 9-membered heterocycle. Preferably the Z ring system is a 5-, 6-, or 7-membered heterocycle, more preferably a 5- or 6-membered heterocycle.

At the 1-position of the ring system is the V heteroatom which is a nitrogen atom. The Z ring optionally contains one or more heteroatoms or heteromoieties (herein collectively described as heteroatoms for simplicity) in addition to the V nitrogen wherein the additional heteroatoms are selected from oxygen (O), nitrogen (N), sulfur (S), sulfoxide (S(O)), sulfone (S(O)₂), and phosphonate (P(O)OK). Preferably the additional heteroatoms are selected from the group consisting of O, N, S, S(O), and S(O)₂, but more preferably Z does not contain any heteroatoms other than the V nitrogen at the 1-position. At the 3-position of the ring system is the Q moiety which is from CH₂, CHR₇, NR₇, S, S(O), and S(O)₂, preferably CH₂, CHR₇, NR₇, and more preferably CH₂ and CHR₇. Most preferably, the Q moiety is CH₂.

Of course, wherein N is an additional heteroatom and also wherein Q is N, the additional N heteroatom and/or Q must be substituted, most preferably with hydrogen or alkyl. The S(O), S(O)₂, and P(O)OK heteroatoms are depicted below in Table 1 for clarity:

TABLE 1



The G Moiety

The G moiety is attached to the —SO₂— moiety and is selected from alkyl having at least 3 carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl,

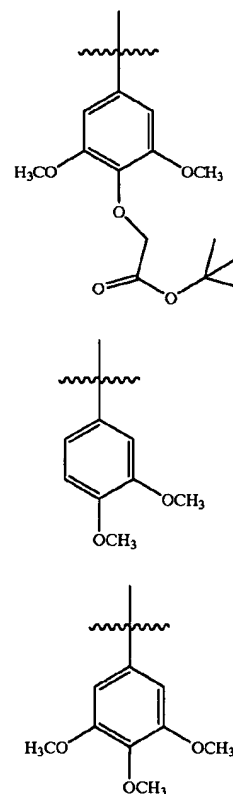
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aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl. The G moiety is preferably substituted with at least one substituent other than hydrogen. In addition to the substituents defined herein which can substitute all moieties, the substituents oxo, amido, —O-alkyl-C(O)OR₃₂, and —O-alkyl-C(O)NHR₃₂, wherein R₃₂ is selected from hydrogen and alkyl, may also substitute on the G moiety.

The G moiety is preferably selected from alkyl having at least 3 carbon atoms, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, and heteroarylalkyl, even more preferably aryl, arylalkyl, and heteroarylalkyl, most preferably aryl. The most preferred aryl for the G moiety is substituted aryl (most preferably substituted phenyl), particularly aryl having at least one alkoxy substituent. Particularly preferred G moieties are shown below in Table 2.

TABLE 2

Preferred G Moieties



The A—X—Y—R₄ Moiety

At the 2-position of the Z ring is the A—X—Y—R₄ moiety which is substituted, as described herein, by R₂, R₃, R₅, and R₆.

The A moiety of the side chain is selected from nil and alkyl. However, wherein A is nil and X is C(O), at least one of the ring substituents R₇, R₈, R₉, and R₁₀ (each of which are described more fully herein below) is not nil or hydrogen. Most preferably, the A moiety is nil, meaning that most preferably, at least one of R₇, R₈, R₉, and R₁₀ is not nil or hydrogen. Of course, wherein A is nil, X is directly attached to the Z ring.

The X moiety of the side chain is dependent upon the structure of the Y moiety and vice versa. X and Y are each,

independently, selected from C(O) (i.e., carbonyl), N, O, S, with the following limitations:

- (i) when X is C(O) then R₃ is nil and Y is selected from N, O, and S;
- (ii) when X is N then R₃ is selected from hydrogen, alkyl, and arylalkyl, Y is C(O), and R₂ is nil;
- (iii) when X is O then R₃ is nil, Y is C(O), and R₂ is nil; and
- (iv) when X is S then R₃ is nil, Y is C(O), and R₂ is nil;

Preferably, X and Y are each, independently, selected from C(O), N, and O. More preferably, X and Y are each, independently, selected from C(O) and N.

X and Y are substituted by R₃ and R₂, respectively. R₃ and R₂ are each, independently, selected from nil, hydrogen, alkyl, and arylalkyl. Wherein X is O or S, then R₃ is nil, and wherein Y is O or S, then R₂ is nil. Wherein X is N, then R₃ is selected from hydrogen, alkyl, and arylalkyl, preferably hydrogen and alkyl, most preferably hydrogen. Wherein Y is N, then R₂ is selected from hydrogen, alkyl, and arylalkyl, preferably hydrogen and alkyl, most preferably hydrogen.

The R₄ moiety is an alkyl moiety. The preferred alkyl moieties follow the preferred limitations set forth above, with the most preferred R₄ moiety being a methylene or methyne group (i.e., a C₁ moiety bearing only one hydrogen substituent).

The R₅ and R₆ moieties are each directly attached to R₄. R₅ and R₆ are each, independently, selected from nil, hydrogen, alkyl having at least three carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; or wherein R₅ and R₆ are bonded together to form a carbocyclic or heterocyclic ring; wherein at least one of R₅ or R₆ is not nil or hydrogen.

Preferably, R₅ and R₆ are each, independently, selected from nil, hydrogen, alkyl having at least three carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; wherein at least one of R₅ or R₆ is not nil or hydrogen. More preferably, R₅ and R₆ are each, independently, selected from alkyl having at least three carbon atoms, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, and heteroarylalkyl. Most preferably, R₅ and R₆ are each, independently, arylalkyl. It is often preferred that R₅ and R₆ are equivalent moieties. Of course, R₅ and R₆ may be each, independently, substituted. Exemplary R₅ and R₆ moieties are shown in Table 3 below.

TABLE 3

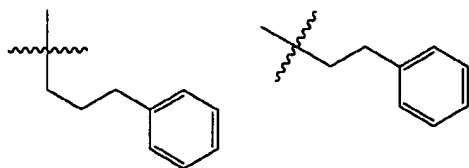
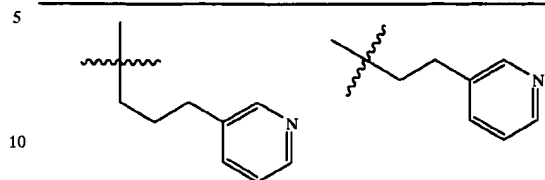
Exemplary R₅ and R₆ Moieties

TABLE 3-continued

Exemplary R₅ and R₆ Moieties

The W Moiety

15 The Z ring may be substituted at the 2-position by an additional moiety, W. The W moiety is selected from nil, hydrogen, and lower alkyl, preferably hydrogen and lower alkyl, most preferably hydrogen. Wherein W is lower alkyl, W is most preferably methyl.

20 The Z Ring Substituents R₇, R₈, R₉ and R₁₀

In addition to the aforementioned substituents at positions 1 and 2 of the Z ring, the Z ring may also have additional substituents at the other available positions, such additional substituents being defined as R₇, R₈, R₉, and R₁₀. These substituents R₇, R₈, and R₉, and R₁₀ are each, independently, selected from nil, hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, halo, cyano, hydroxy, oxo, imino, —R₁₄SR₁₅, —R₁₄S(O₂)R₁₅, —R₁₄S(O)R₁₅, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄C(O)OR₁₅, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, —R₁₄P(O)NR₁₅R₁₆, —R₁₄P(O)OR₁₅R₁₆, and a spiro moiety, and wherein R₇ and R₈ may be optionally bonded together to form an aromatic or saturated, carbocyclic or heterocyclic ring wherein the ring is fused to Z; wherein when A is nil and X is C(O) at least one of R₇, R₈, R₉, and R₁₀ is not nil or hydrogen. R₁₄ and R₁₅ are each, independently, selected from nil, hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl. R₁₆ is selected from hydrogen and alkyl.

Preferably, R₇, R₈, and R₉, and R₁₀ are each, independently, selected from nil, hydrogen, alkyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, halo, hydroxy, oxo, —R₁₄SR₁₅, —R₁₄S(O₂)R₁₅, —R₁₄S(O)R₁₅, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, and a spiro moiety, and wherein R₇ and R₈ may be optionally bonded together to form an aromatic or saturated, carbocyclic or heterocyclic second ring wherein the second ring is fused to Z. More preferably, R₇, R₈, and R₉, and R₁₀ are each, independently, selected from nil, hydrogen, alkyl, heteroalkyl, heteroalkenyl, aryl, arylalkyl, heteroarylalkyl, halo, hydroxy, oxo, —R₁₄SR₁₅, —R₁₄S(O₂)R₁₅, —R₁₄S(O)R₁₅, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, and a spiro moiety, and wherein R₇ and R₈ may be optionally bonded together to form an aromatic or saturated, carbocyclic or heterocyclic second ring wherein the second ring is fused to Z. Even more preferably, R₇, R₈, and R₉, and R₁₀ are each, independently, selected from nil, hydrogen, alkyl, heteroalkyl, heteroalkenyl, aryl, arylalkyl, heteroarylalkyl, halo, hydroxy, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, and a spiro moiety, and wherein R₇ and R₈ may be optionally bonded together to form an aromatic or saturated, carbocyclic or heterocyclic second ring wherein the second ring is fused to Z. Most preferably, R₇ and R₈ are bonded together to form an

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aromatic or saturated (preferably aromatic), carbocyclic or heterocyclic (preferably carbocyclic) second ring wherein the second ring is fused to Z.

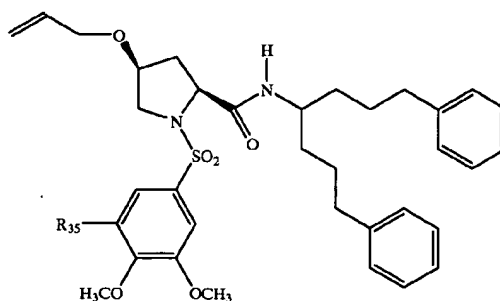
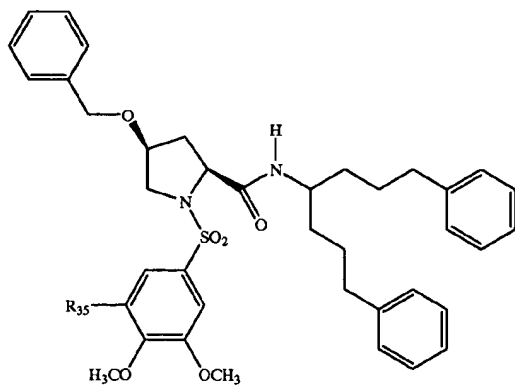
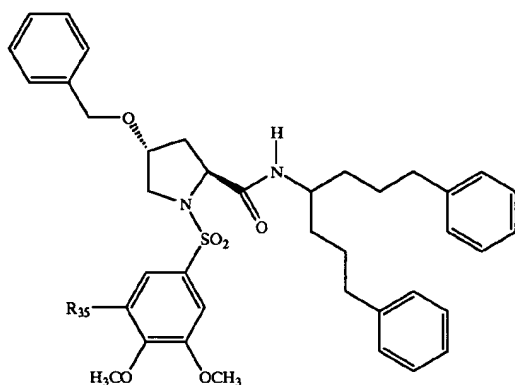
Wherein R_7 and R_8 are bonded together to form an aromatic or saturated, carbocyclic or heterocyclic second ring wherein the second ring is fused to Z, the second ring may, of course, be substituted or unsubstituted. A preferred second ring is phenyl.

Preferably, at least one of R_7 , R_8 , R_9 , and R_{10} is not nil or hydrogen.

Exemplary compounds of the present invention are presented in the following tables.

TABLE 4

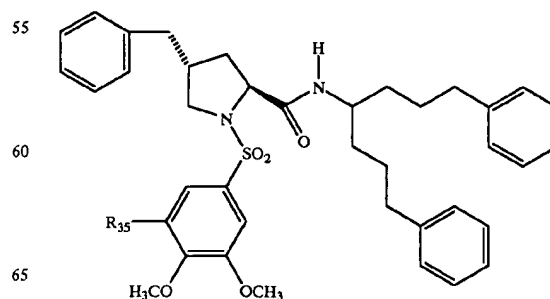
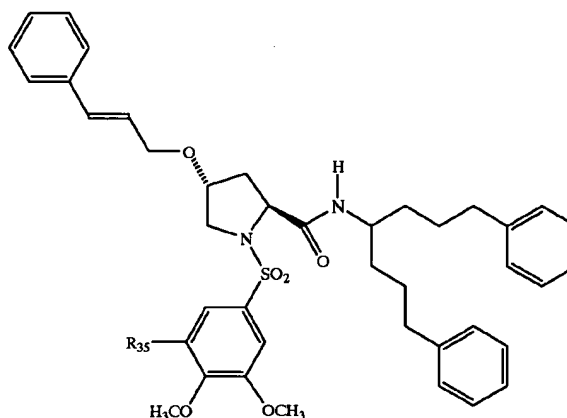
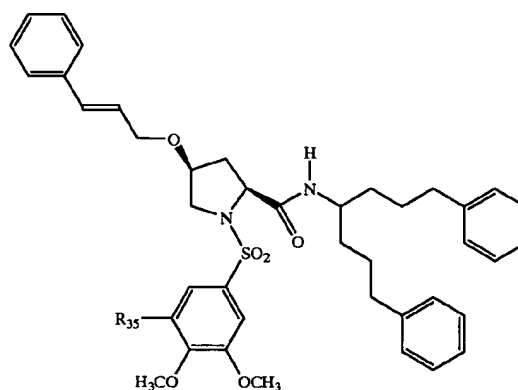
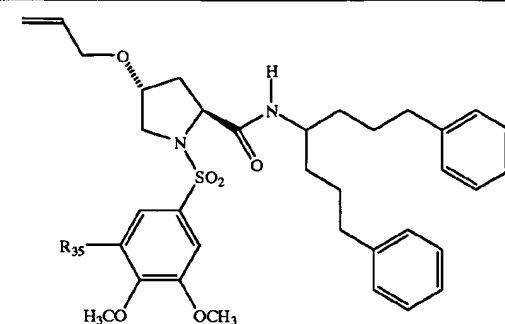
Exemplary Compounds of the Present Invention



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TABLE 4-continued

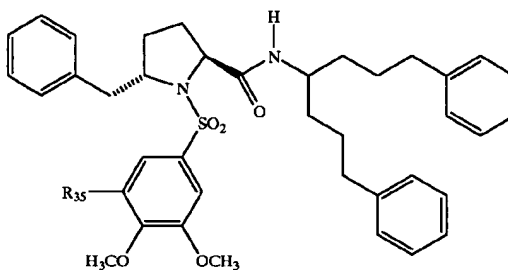
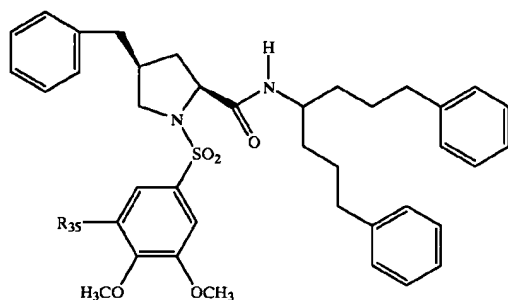
Exemplary Compounds of the Present Invention



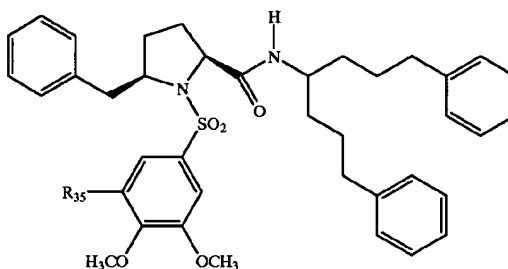
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TABLE 4-continued

Exemplary Compounds of the Present Invention



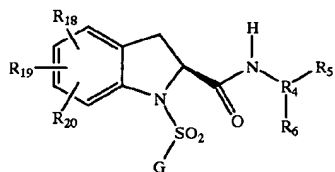
and



wherein in Table 4, R_{35} is selected from hydrogen and $-OR_{36}$, wherein R_{36} is selected from hydrogen and alkyl.

TABLE 5

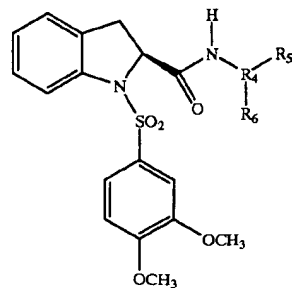
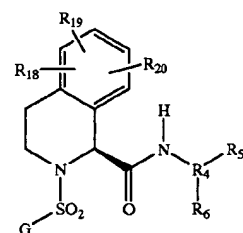
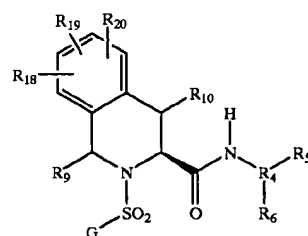
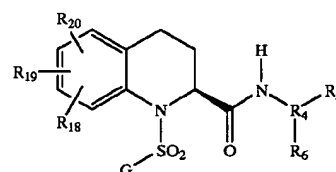
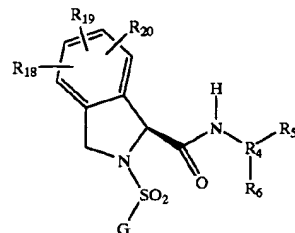
Exemplary Compounds of the Present Invention



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TABLE 5-continued

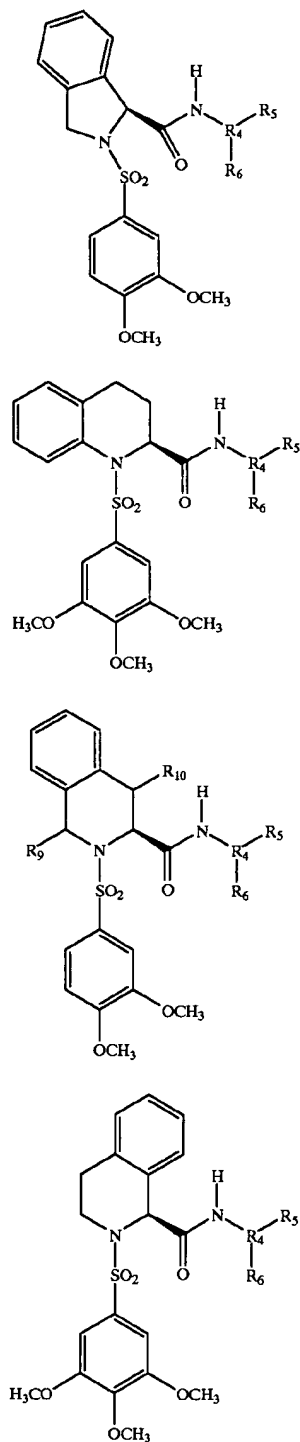
Exemplary Compounds of the Present Invention



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TABLE 5-continued

Exemplary Compounds of the Present Invention

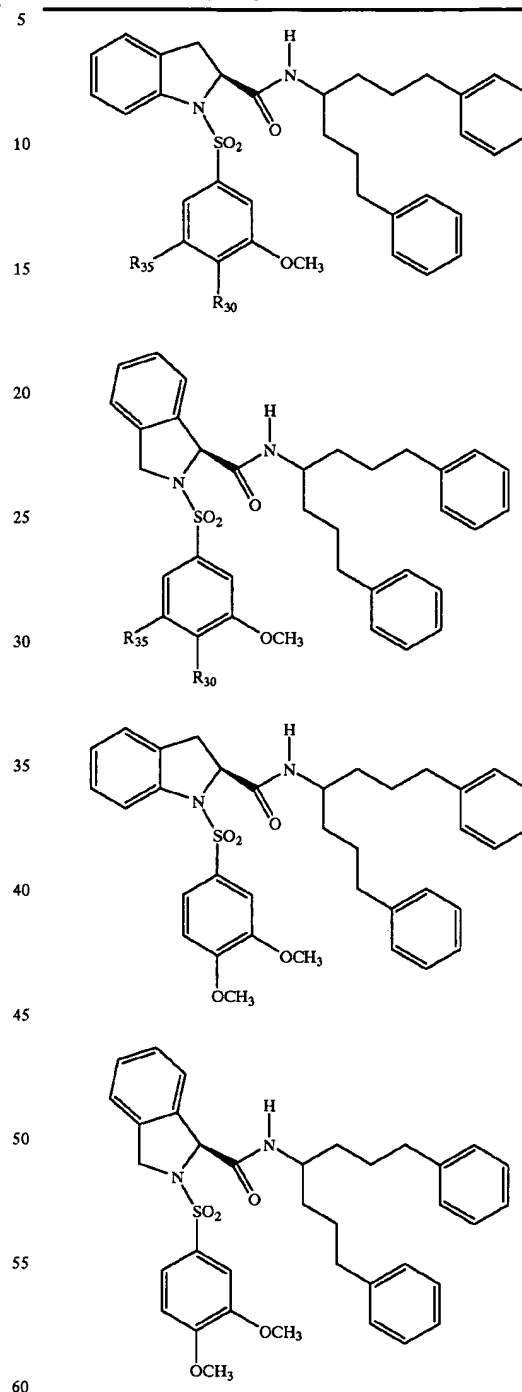


wherein, in Table 5, R₁₈, R₁₉, and R₂₀ are each, independently, selected from hydrogen, alkoxy, aryloxy, hydroxy, nitro, amino, halo, and thiol.

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TABLE 6

Exemplary Compounds of the Present Invention

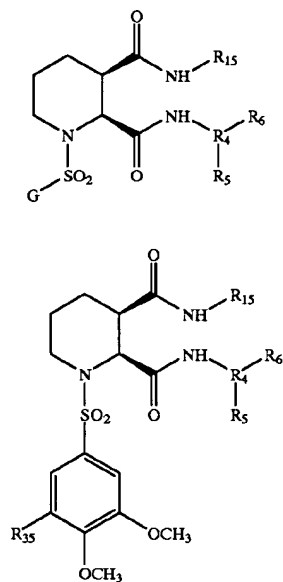


wherein in Table 6, R₃₀ is selected from —OR₃₂ and —OCH₂C(O)OR₃₂, wherein R₃₂ is selected from hydrogen and alkyl, and wherein R₃₅ is selected from hydrogen and —OR₃₆, wherein R₃₆ is selected from hydrogen and alkyl.

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TABLE 7

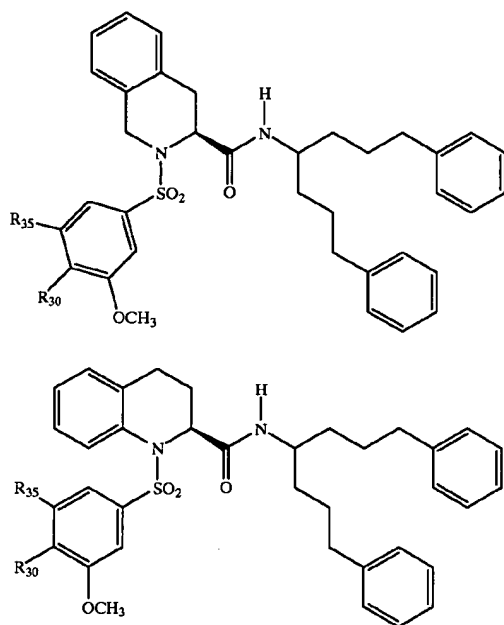
Exemplary Compounds of the Present Invention



wherein in Table 7, R_{35} is selected from hydrogen and $-OR_{36}$, wherein R_{36} is selected from hydrogen and alkyl.

TABLE 8

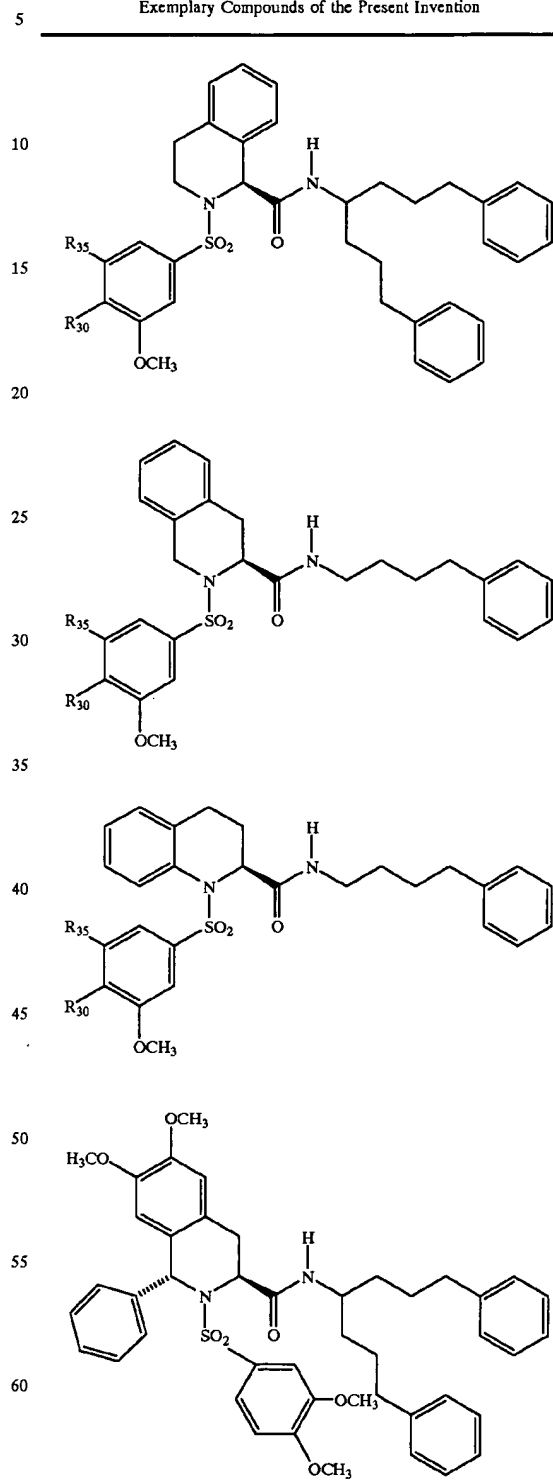
Exemplary Compounds of the Present Invention



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TABLE 8-continued

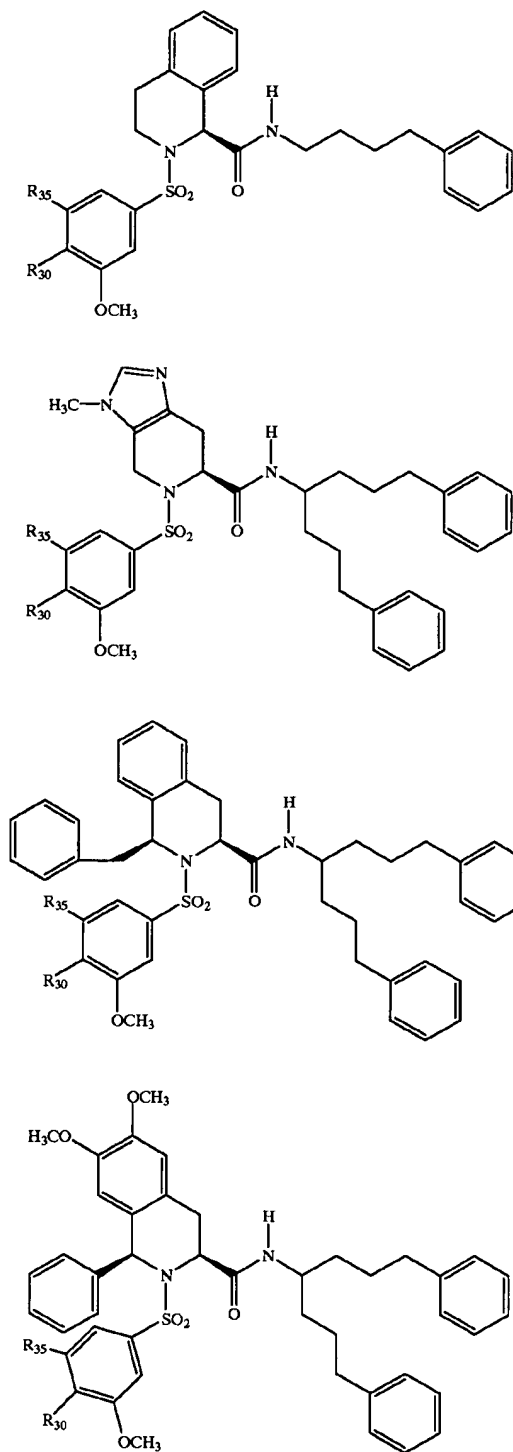
Exemplary Compounds of the Present Invention



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TABLE 8-continued

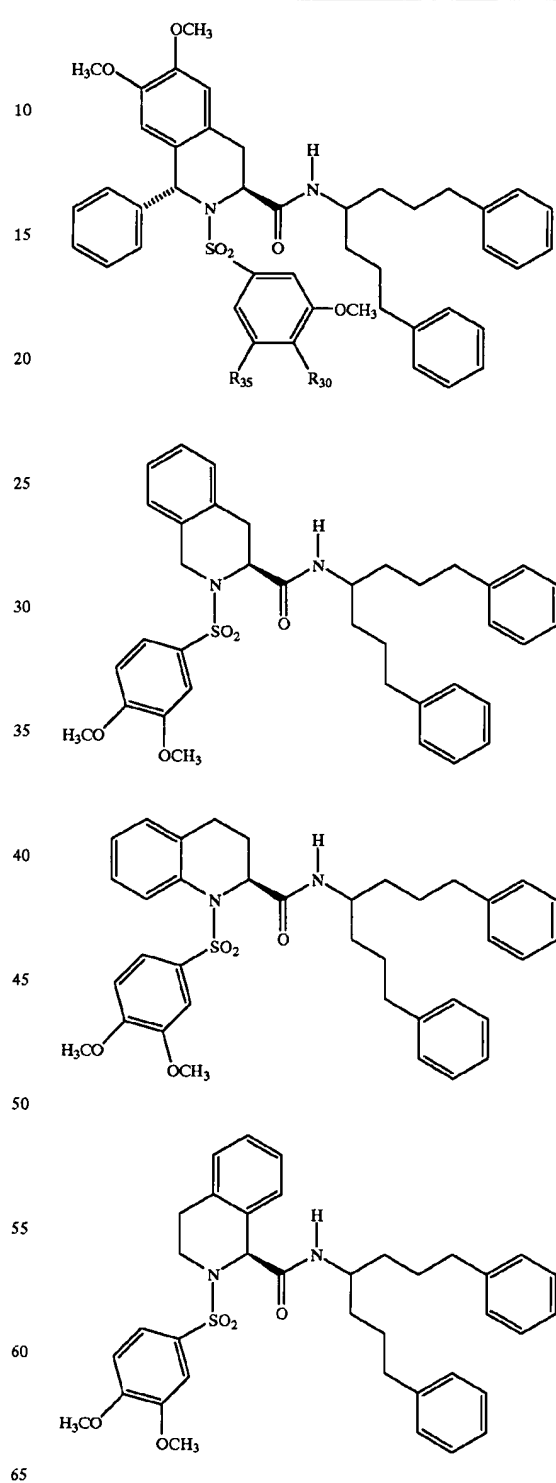
Exemplary Compounds of the Present Invention



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TABLE 8-continued

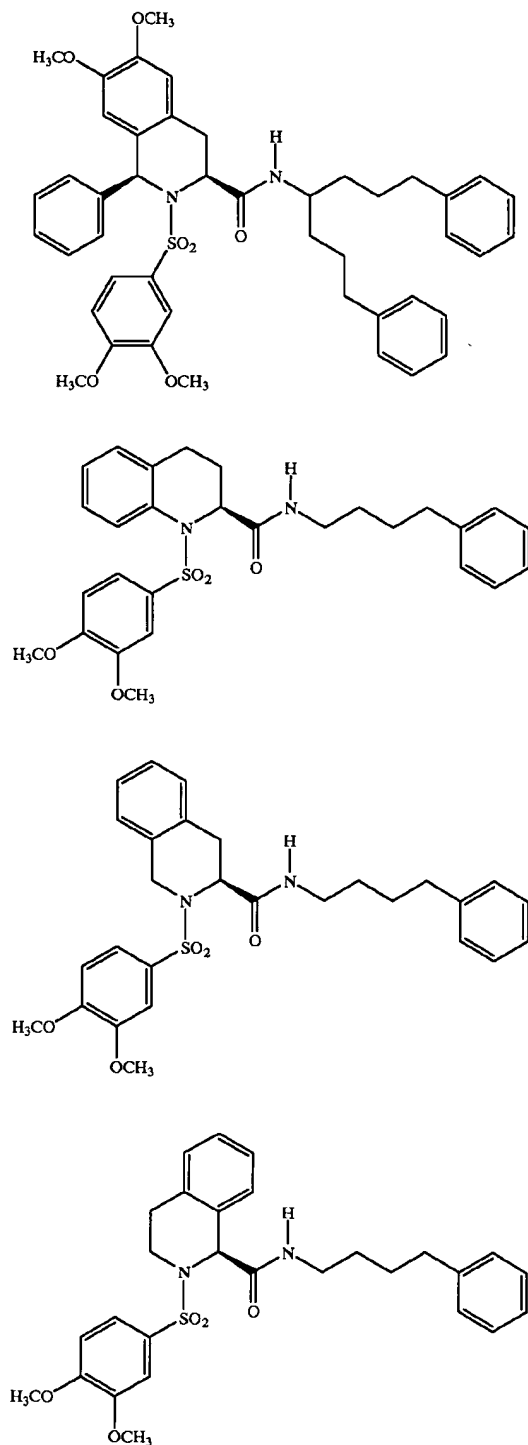
Exemplary Compounds of the Present Invention



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TABLE 8-continued

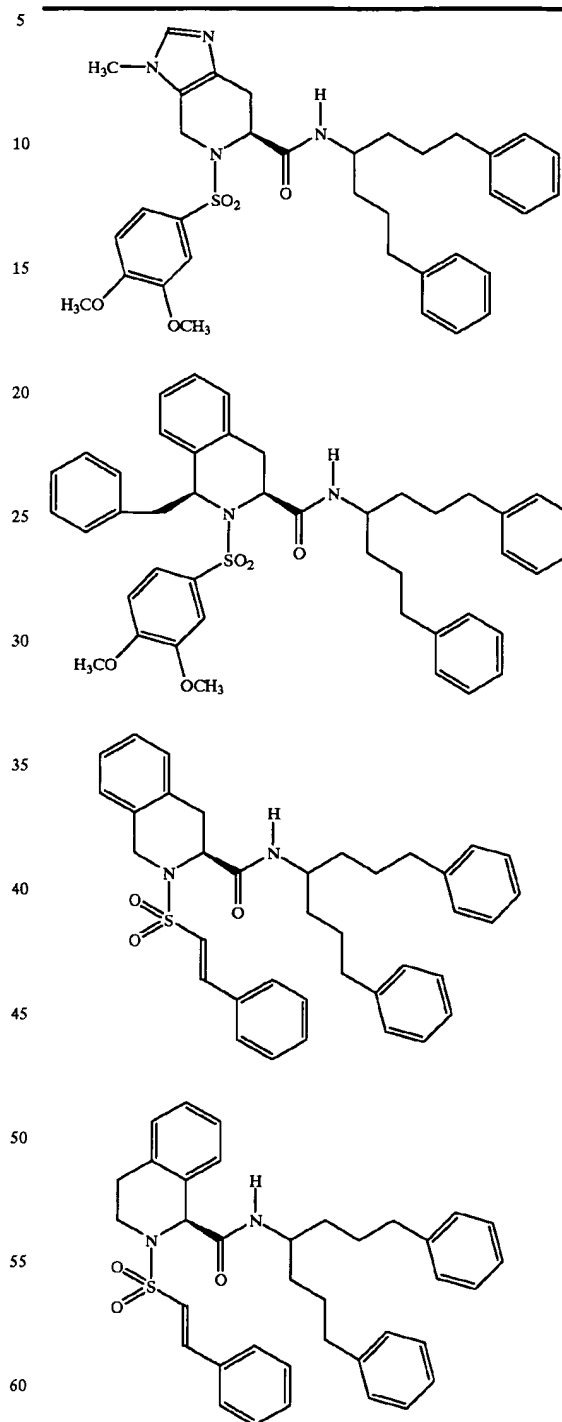
Exemplary Compounds of the Present Invention



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TABLE 8-continued

Exemplary Compounds of the Present Invention



wherein in Table 8, R_{30} and R_{35} are each, independently, selected from $-OR_{32}$ and $-OCH_2C(O)OR_{32}$, wherein R_{32} is selected from hydrogen and alkyl.

The present compounds are hair growth actives, the more preferred among these being non-immunosuppressive. The compounds (test compounds) of the present invention may be tested for their ability to induce anagen and their immunosuppressive activity (or lack thereof) using the following methods. Alternatively, other methods well-known in the art may be used (but with the term "non-immunosuppressive" being defined according to the method disclosed herein).

Telogen Conversion Assay

The Telogen Conversion Assay measures the potential of a test compound to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair (fur) growth wherein the topical application of hair growth promoters are evaluated. The Telogen Conversion Assay herein below is used to screen compounds for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are utilized: a vehicle control group, a positive control group, and a test compound group, wherein the test compound group is administered a compound of the present invention. The length of the assay is at least 19 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. Most studies will end on Day 19, but a few may be carried out to Day 24 if the melanogenesis response looks positive, but occurs slowly. A typical study design is shown in Table 9 below:

TABLE 9

Group #	Animal #	Compound	Concentration	Application volume	Length of Study
1	1-10	Test Compound	5% in vehicle**	400 μ L topical	19 or 24 days
2	11-20	Cyclosporin A	0.19% in vehicle**	400 μ L topical	19 or 24 days
3	21-30	Vehicle**	N/A	400 μ L topical	19 or 24 days

**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 μ L to each mouse's back. The 400 μ L application is applied slowly while moving hair on the mouse to allow the application to reach the skin.

While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As the mice convert from telogen to anagen their skin color will become more bluish-black. As indicated in Table 10, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black:

TABLE 10

Visual Observation	Grade
Whitish Skin Color	0
Skin is light gray (indication of initiation of anagen)	1
Appearance of Blue Spots	2
Blue Spots are aggregating to form one large blue area	3
Skin is dark blue (almost black) with color covering majority of treatment area (indication of mouse in full anagen)	4

Immunosuppression Assay

The immunosuppression assay herein predicts the immunosuppressive activity of a compound of the present invention. The assay is performed as follows:

Spleens are excised from euthanized (CO₂ asphyxiation) adult male C3H mice ranging in age from seven to sixteen weeks old (live mice commercially available from Harlan Sprague Dawley, Inc., Indianapolis, Ind.). The spleens are placed immediately in cold Hanks Balanced Salt Solution (HBSS, commercially available from Gibco-BRL, Gaithersburg, Md.). The spleens are then ground up between frosted glass slides and filtered through a sterile screen to remove tissue debris. The resulting cell suspension is underlaid with an equal volume of Ficoll-Paque Plus (commercially available from Pharmacia Biotech, Piscataway, N.J.) and centrifuged at 400x g for approximately forty minutes at 20° C. in order to collect the splenocytes. The splenocytes are collected from the interface using a disposable pipet and are washed twice with HBSS, followed by centrifugation at 100x g for ten min at 20° C. Splenocytes are resuspended in five to ten mL of cell culture media consisting of phenol red-free RPMI 1640 (culture media commercially available from Gibco-BRL) containing 10% heat-inactivated fetal bovine serum (Gibco-BRL), penicillin (50 U/mL), streptomycin (100 μ g/mL), L-glutamine (2 mM), 2-mercaptoethanol (10⁻⁵ M), and N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10 mM). The cells are counted and checked for viability using, for example, trypan blue. Splenocytes are resuspended in medium at 10⁶ cells/mL and pipetted into 96 well round bottom plates at 10⁵ cells/well. Splenocytes are activated by addition of 50 μ L/well of concanavalin A (final assay concentration=5 μ g/ml) in the presence or absence of a test compound. Test compounds are made up as stock solutions in methyl sulfoxide (DMSO), then diluted in medium and 50 μ L/well added, such that the final concentration of DMSO in the assay is below 0.05%. The plates are incubated at 37° C. with 5% CO₂ for 48 hours. After 48 hours, the cells are pulsed with 1 μ Ci/well of methyl-³H-thymidine (commercially available from Amersham, Buckinghamshire, England) and incubated an additional 24 hours.

After 24 hours, the cells are harvested onto GF/C filter plates (commercially available from Packard, Downers Grove, Ill.), solubilized in Microscint 20 (Packard), and counted on a TopCount microplate scintillation and luminescence plate counter (Packard). Activity is measured as a percentage of control activity in the absence of test compound and plotted versus test compound concentration. The data are fit to a 4-parameter curve fit (Sigmaplot) and IC₅₀ values are calculated. As used herein, test compounds are considered non-immunosuppressive if, by using this method, the ratio of (cyclosporin A IC₅₀/test compound IC₅₀) \times 100 is less than or equal to 0.02, i.e., a non-immunosuppressive test compound has \leq 2% of the immunosuppressive activity of cyclosporin A.

Cell viability is assessed using the MTT (3-[4,5-dimethylthiazoyl-2-yl]2,5-diphenyl-tetrazolium bromide) dye assay

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as described by Nelson et al., *Journal of Immunology*, Vol. 150, No. 6, pp. 2139-2147 (1993), with the exception that the assay is carried out in serum-free, phenol red-free RPMI 1640 and the dye is solubilized in 100 μ L/well DMSO and read at an OD of 540 nm with a background correction at 650 nm on a SpectraMax Plus microplate reader (Molecular Devices, Menlo Park, Calif.).

Multi-Drug Resistance

As disclosed herein, the present compounds are also useful, for example, to increase the antiproliferative activity of a drug and/or prevent and/or treat multi-drug resistance. The present compounds may be assayed for this property as described in U.S. Pat. No. 5,744,485, Zelle et al., assigned to Vertex Pharmaceuticals Inc., issued Apr. 28, 1998, U.S. Pat. No. 5,726,184, Zelle et al., assigned to Vertex Pharmaceuticals Inc., issued Mar. 10, 1998, U.S. Pat. No. 5,620,971, Armistead et al., assigned to Vertex Pharmaceuticals Inc., issued Apr. 15, 1997, and U.S. Pat. No. 5,543,423, Zelle et al., assigned to Vertex Pharmaceuticals Inc., issued Aug. 6, 1996.

Methods of Making

The compounds of the present invention are prepared according to methods which are well-known to those skilled in the art. The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, *Advanced Organic Chemistry*, John Wiley & Sons, 1992.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and/or avoiding any undesirable side reactions. Often, the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many such manipulations can be found in, for example, T. Greene, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, 1981.

The compounds of the present invention may have one or more chiral center. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

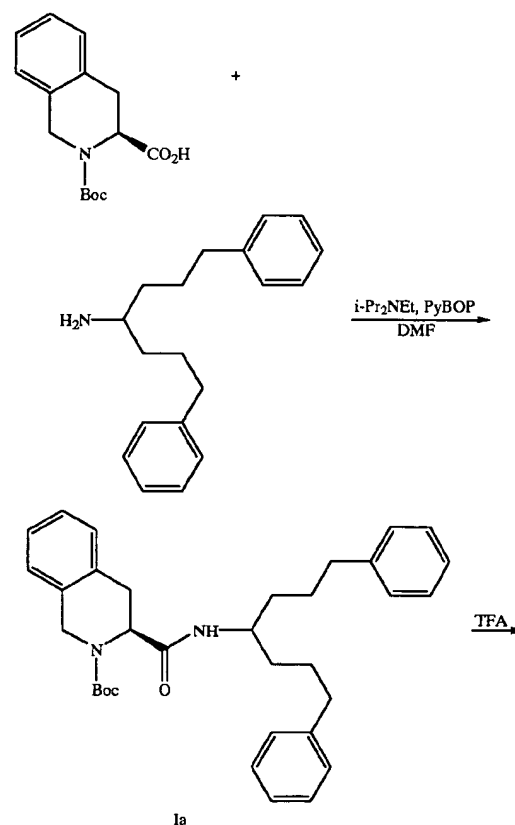
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The following provides non-limiting examples illustrating more specifically the methods of making various compounds of the present invention.

As used herein, the following abbreviations are used:

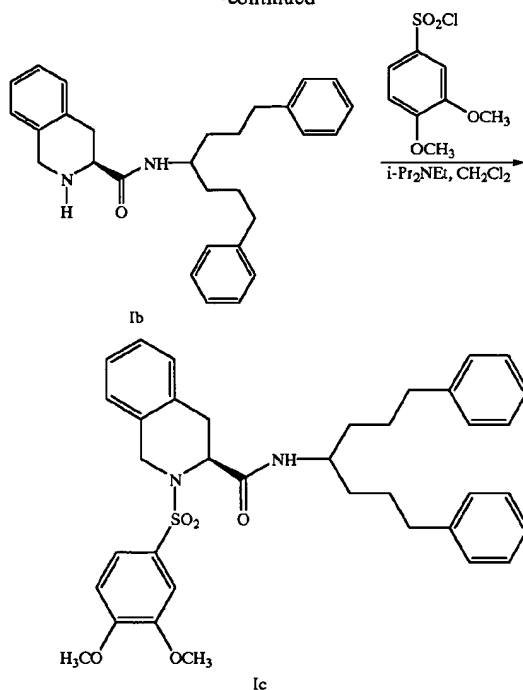
Reagent	Abbreviation
N,N-dimethylformamide	DMF
1-hydroxybenzotriazole hydrate	HOBt
tert-butoxycarbonyl	BOC
(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (commercially available from Fluka Chemical, Switzerland)	PyBOP
tetrahydrofuran	THF
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	EDAC
trimethylsilyl trifluoromethanesulfonate	TMS-OTf
N,N-diisopropylethylamine	i-Pr ₂ NEt or i-Pr ₂ EtN
trifluoroacetic acid	TFA
lithium hydroxide	LiOH

EXAMPLE 1



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-continued



1a. (S)-(N-tert-Butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid 1,7-diphenyl-4-heptylamide

(S)-(N-tert-Butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (4.90 g, 17.7 mmol) is dissolved in 160 mL of DMF. 1,7-Diphenyl-4-aminoheptane (4.30 g, 16.1 mmol) and N,N-diisopropylethylamine (4.16 g, 32.2 mmol) are added followed by PyBOP (8.80 g, 16.9 mmol). The reaction is stirred for 18.5 hours at room temperature, then poured onto ice-cold 0.1N HCl (600 mL)

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and extracted with ethyl acetate (600 mL). The organic layer is washed successively with brine (100 mL), saturated NaHCO₃ solution (300 mL), and brine (2×200 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product by chromatography on silica gel (8:2 hexane:ethyl acetate) affords the desired amide 1a.

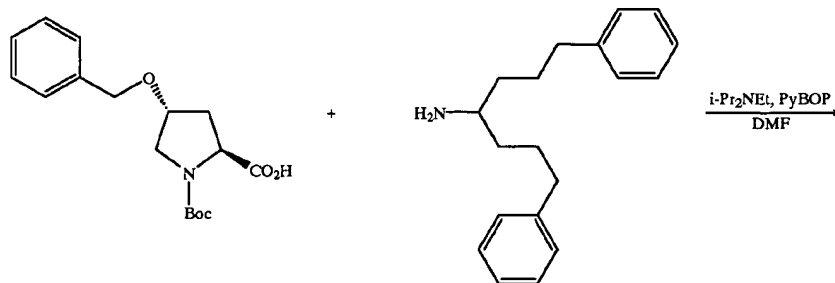
1b. (S)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid 1,7-diphenyl-4-heptylamide

The amide 1a (8.07 g, 15.3 mmol) is dissolved in 150 mL of anhydrous dichloromethane. Trifluoroacetic acid (120 mL) is added dropwise over a five minute period. After 2 hours the mixture is cooled in an ice-bath and saturated K₂CO₃ solution is added until the pH is approximately 8. The mixture is transferred to a separatory funnel containing dichloromethane (200 mL) and water (200 mL) and shaken. The organic layer is washed with water (200 mL) before drying over MgSO₄. The mixture is filtered and concentrated under reduced pressure to afford the desired amine 1b.

1c. (S)-N-(3',4'-Dimethoxyphenylsulfonyl)-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid 1,7-diphenyl-4-heptylamide

The amide 1b (5.0 g, 11.7 mmol) is dissolved in anhydrous methylene chloride (100 mL) at room temperature. N,N-diisopropylethylamine (2.55 mL, 14.7 mmol) is added and the solution is cooled to 5° C. 3',4'-Dimethoxyphenylsulfonyl chloride (3.47 g, 14.7 mmol) is added in one portion. The reaction mixture is stirred for 18 hours at room temperature then concentrated to one-half volume. The concentrate is poured onto ethyl acetate (300 mL) and washed successively with 0.1M HCl (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (50 mL). The organic solution is dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the crude product by preparative chromatography (silica gel; gradient elution with 4:1 to 1:1 hexane:ethyl acetate) affords the desired sulfonamide 1c.

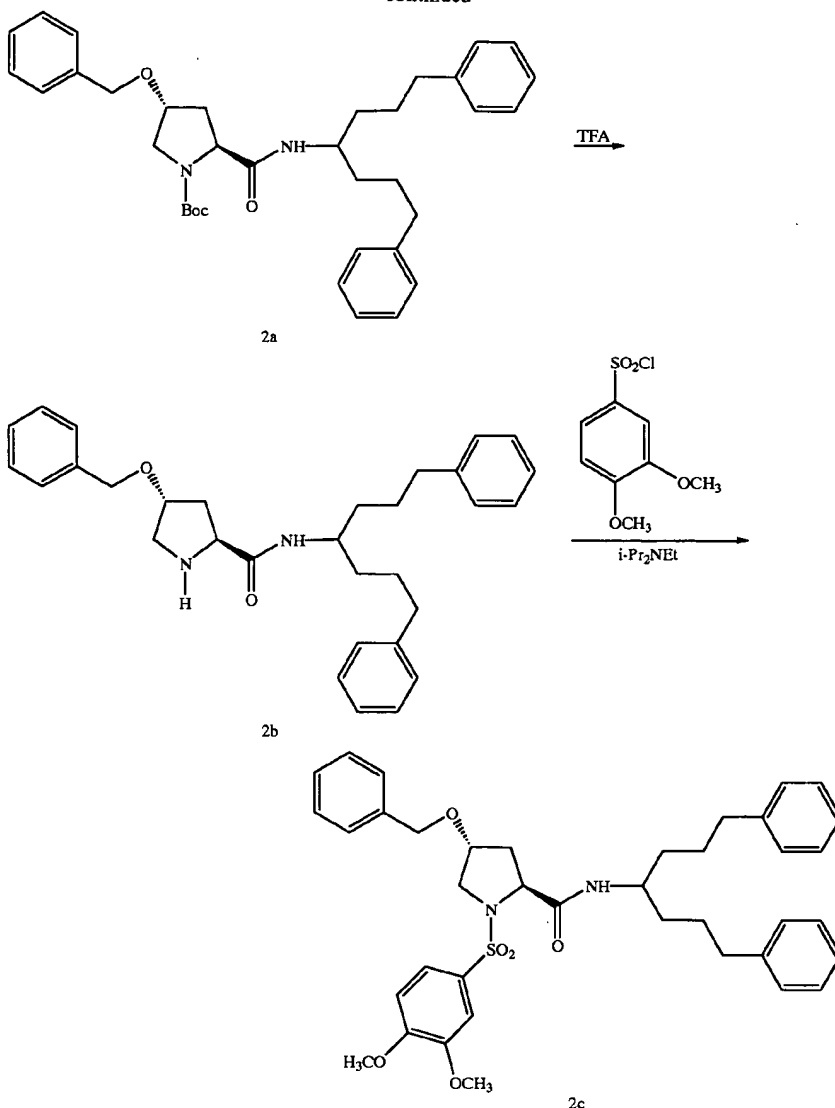
EXAMPLE 2



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-continued



2a (N-tert-Butoxycarbonyl)-4(R)-benzyloxypyrrolidine-2(S)-carboxylic acid 1,7-diphenyl-4-heptylamide

(N-tert-Butoxycarbonyl)-4(R)-benzyloxypyrrolidine-2(S)-carboxylic acid (5.68 g, 17.7 mmol) is dissolved in 160 mL of DMF. 1,7-Diphenyl-4-aminoheptane (4.30 g, 16.1 mmol) and N,N-diisopropylethylamine (4.16 g, 32.2 mmol) are added followed by PyBOP (9.20 g, 17.1 mmol). The reaction is stirred for 20.5 hours at room temperature, then poured onto ice-cold 0.1N HCl (600 mL) and extracted with ethyl acetate (600 mL). The layers are separated and the organic layer washed successively with brine (100 mL), saturated NaHCO₃ solution (300 mL), and brine (2x200 mL). The organic solution is dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the product on silica gel (7:3 hexane:ethyl acetate) affords the desired amide 2a.

2b. 4(R)-benzyloxypyrrolidine-2(S)-carboxylic acid 1,7-diphenyl-4-heptylamide

The amide 2a (9.04 g, 16.5 mmol) is dissolved in 160 mL of anhydrous dichloromethane. Trifluoroacetic acid (130 mL) is added dropwise over a 5 minute period. After 45 minutes the mixture is cooled in an ice-bath and saturated K₂CO₃ solution is added until the pH is approximately 8. The mixture is transferred to a separatory funnel containing dichloromethane (300 mL) and water (300 mL) and shaken. The organic layer is washed with water (100 mL) before drying over MgSO₄. The mixture is filtered and concentrated under reduced pressure to afford the desired amine 2b.

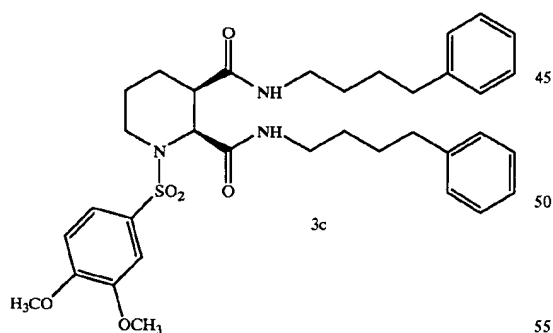
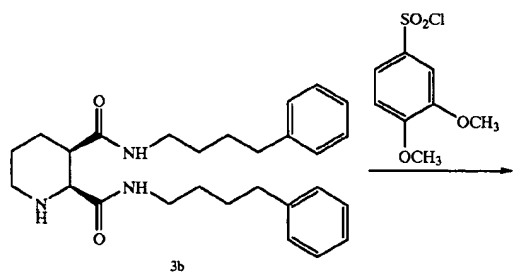
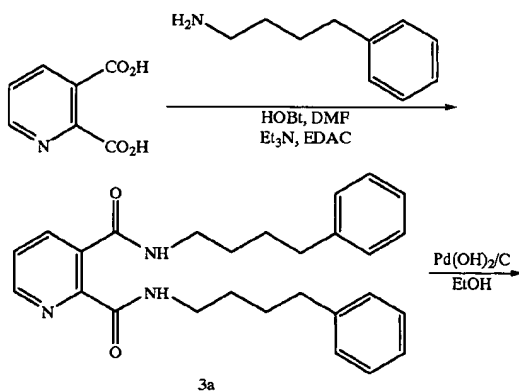
2c. N-(3',4'-Dimethoxyphenylsulfonyl)-4(R)-benzyloxypyrrolidine-2(S)-carboxylic acid 1,7-diphenyl-4-heptylamide

The amine 2b (5.65 g, 12.0 mmol) is taken up in anhydrous methylene chloride (100 mL) at room temperature.

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N,N-diisopropylethylamine (2.6 mL, 15 mmol) is added and the solution is cooled to 5° C. 3',4'-Dimethoxyphenylsulfonyl chloride (3.5 g, 15 mmol) is added in one portion. The reaction mixture is stirred for 18 hours at room temperature then concentrated to one-half volume. The concentrate is poured onto ethyl acetate (300 mL) and washed successively with 0.1 M HCl (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (50 mL). The organic solution is dried, filtered, and concentrated in vacuo. Purification of the crude product by preparative chromatography affords the desired sulfonamide 2c.

EXAMPLE 3



3a. 2,3-Pyridinedicarboxylic acid bis(1-phenylbutylamide)

2,3-Pyridinedicarboxylic acid (3.0 g, 18.0 mmol) is combined with 1-hydroxybenzotriazole (7.29 g, 54 mmol) at ambient temperature under inert atmosphere. Anhydrous DMF (150 mL) is added followed by 4-phenylbutylamine (6.24 mL, 39 mmol), triethylamine (5.0 mL, 36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.61 g, 45 mmol) in succession. The reaction

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mixture is stirred for 18 hours at ambient temperature under inert atmosphere then poured onto ethyl acetate (500 mL) and extracted successively with water (250 mL), 1N HCl (150 mL), and brine (100 mL). The organic solution is dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford the desired bis-amide 3a.

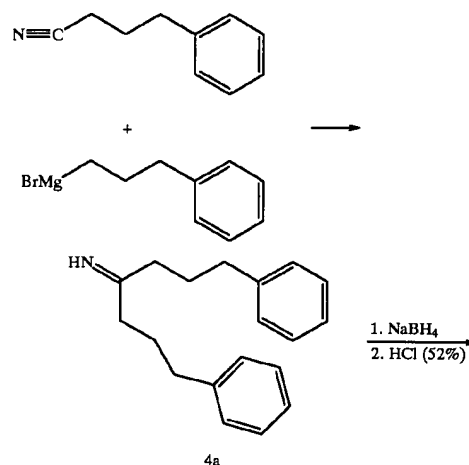
3b. cis-2,3-Piperidinedicarboxylic acid bis(1-phenylbutylamide)

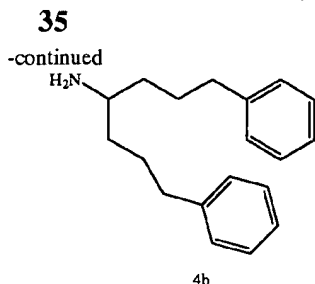
The bis-amide 3a (5.5 g, 12.8 mmol) is dissolved in absolute ethanol (50 mL) at ambient temperature and transferred to a low pressure hydrogenation vessel containing Pearlman's catalyst (20 weight percent $\text{Pd}(\text{OH})_2$ on carbon, 1.0 g). The mixture is hydrogenated at 50 psi until the reduction is complete. The catalyst is removed by filtration through a pad of diatomaceous earth and the filtrate is concentrated under reduced pressure. Purification of the crude product by preparative chromatography (silica gel; gradient elution with 95:5:0.1 to 80:20:0.1 methylene chloride:methanol:concentrated ammonium hydroxide) affords the desired piperidine bis-amide 3b.

3c. N-(3',4'-Dimethoxyphenylsulfonyl)-cis-2,3-piperidine dicarboxylic acid bis(1-phenylbutylamide)

The piperidine bis-amide 3b (2.12 g, 4.87 mmol) is taken up in anhydrous methylene chloride (100 mL) at room temperature. N,N-Diisopropylethylamine (1.1 mL, 6 mmol) is added and the solution is cooled to 5° C. 3',4'-Dimethoxyphenylsulfonyl chloride (1.4 g, 6 mmol) is added in one portion. The reaction mixture is stirred for 18 hours at room temperature then concentrated to one-half volume. The concentrate is poured onto ethyl acetate (120 mL) and washed successively with 0.1 M HCl (40 mL), saturated sodium bicarbonate solution (40 mL), and brine (20 mL). The organic solution is dried, filtered, and concentrated in vacuo. Purification of the crude product by preparative chromatography affords the desired sulfonamide 3c.

EXAMPLE 4





4a. Magnesium (40.2 g, 1.65 mol) and anhydrous ether (3.2 L) are combined in a reaction vessel with stirring. A solution of 1-bromo-3-phenyl propane in 1.6 L of anhydrous ether is added to an addition funnel. The bromide solution is added dropwise to the stirring reaction vessel over a 1 hour period. Upon completion of addition, the mixture stirs for 1–2 hours. A solution of 4-phenylbutyronitrile (160 g, 1.1 mol) in anhydrous ether (2.4 L) is placed in the addition funnel. The solution is added to the reaction vessel over a 1 hour time period. Upon complete addition the solution is heated to reflux for 10 hours, and then stirs at room temperature for six hours.

4b. 1,7-Diphenyl-4-aminoheptane

The reaction mixture of 4a is diluted with methanol (3.2 L) using an addition funnel. Sodium borohydride (83.4 g, 2.2 mol) is added in portions. Upon complete addition the reaction is stirred at room temperature for six hours. The reaction mixture is quenched by a slow addition of water (3.2 L). The mixture is diluted with ether (3.2 L) and water (1.6 L). The ether layer is separated and the aqueous layer is extracted twice with ether (3.2 Lx2). The combined ether extracts are washed once with sodium chloride solution, dried, filtered, and concentrated in vacuo to give the crude product. This product is diluted in ether (1.2 L) and acidified by slow addition of 1M HCl (1.2 L). The mixture stirs for one hour and is concentrated in vacuo. The resulting precipitate is diluted with acetonitrile and is stirred for 16 hours. The desired 1,7-Diphenyl-4-aminoheptane 4b is collected by filtration.

Use of the Present Compounds

The compounds herein may be used for the treatment of such conditions as, for example, treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

While certain of the present compounds may exhibit immunosuppressive activity, the preferred compounds of the present invention are, as defined herein, non-immunosuppressive.

Furthermore, in addition to treating hair loss, the compounds of the present invention may be used to treat a variety of clinical conditions which include, but are not limited to, multi-drug resistance (particularly for use in cancer chemotherapy), neurological disorders and neurodegenerative diseases, cardiac injury associated with ischemia/reperfusion injury, and treatment of fungal, microbial, viral (especially HIV), malarial or other parasitic diseases or conditions. The present compounds may also be useful as inhibitors of multi-drug transporter proteins to enhance, for example, pharmacokinetics and bioavailability. Certain compounds of the present invention may exhibit immuno-

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modulatory properties. These compounds would prove useful in the treatment of organ transplant rejection and various autoimmune diseases which include, but are not limited to, Behcet's disease, Crohn's disease, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, eczema, multiple sclerosis, myasthenia gravis, insulin-dependent diabetes mellitus, and Graves' disease. In addition, the present compounds may have utility for the treatment of certain inflammatory and allergic disease states, including urticaria, allergic contact dermatitis, atopic dermatitis, atopic keratoconjunctivitis, inflammatory bowel disease, and asthma. The present compounds may also be useful in the treatment of cardiac hypertrophy in congestive heart failure.

The present compounds may also be useful in combination with a matrix metalloproteinase inhibitor for treatment of various conditions including, for example, tissue destructive diseases mediated by excessive metalloproteinase activity, cancer, and multi-drug resistance, as well as all of the conditions previously mentioned herein above. Particularly preferred matrix metalloproteinase inhibitors useful in such combination include those described in U.S. patent application Ser. No. 60/024,765, Pikul et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,842, Natchus et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,846, Pikul et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,746, Almstead et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,830, Pikul et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,764, De et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, U.S. patent application Ser. No. 60/024,764, De et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996, and U.S. patent application Ser. No. 60/024,766, Wang et al., assigned to The Procter & Gamble Co., filed Aug. 28, 1996.

Preferably, the compounds of the present invention are formulated into pharmaceutical compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa. (1990).

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound of the present invention is administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific compound used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier ("carrier"). The term pharmaceutically-acceptable carrier, as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of

the composition are capable of being commingled with a compound of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal, being treated. The carrier can itself be inert or it can possess pharmaceutical benefits of its own.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical or oral administration is especially preferred. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the activity of the compound of the present invention. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: *Modern Pharmaceutics*, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms*, 2nd Ed., (1976).

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tabletting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of a compound of the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing

suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds

into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, tri-alkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: 1. An in vitro Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404-407 (1993), Wallach and Philippot, "New Type of Lipid Vesicle: Novasome®", *Liposome Technology*, Vol. 1, pp. 141-156 (1993), and Wallach, U.S. Pat. No. 4,911,928, assigned to Micro-Pak, Inc., issued Mar. 27, 1990.

The compounds of the present invention may also be administered by iontophoresis. See, e.g., www.unipr.it/arpa/dipfarm/erasmus/erasm14.html, Banga et al., "Hydrogel-based Iontophoretic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", *Pharm. Res.*, Vol. 10 (5), pp. 697-702 (1993), Ferry L. L., "Theoretical Model of

Iontophoresis Utilized in Transdermal Drug Delivery", *Pharmaceutical Acta Helvetiae*, Vol. 70, pp. 279-287 (1995), Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", *Int. J. Pharm.*, Vol. 123, pp. 159-171 (1995), Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin in vitro", *Pharm. Res.*, Vol. 8, pp. 1121-1127 (1991), Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", *Int. J. Pharm.*, Vol. 120, pp. 221-8 (1995), O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", *Drugs*, Vol. 37, pp. 233-309 (1989), Parry et al., "Acyclovir Bioavailability in Human Skin", *J. Invest. Dermatol.*, Vol. 98 (6), pp. 856-63 (1992), Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", *Pharm. Res.*, Vol. 14 (1), pp. 63-66 (1997), Santi et al., "Reverse Iontophoresis—Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", *J. Control. Release*, Vol. 38, pp. 159-165 (1996), Santi et al., "Reverse Iontophoresis—Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", *J. Control. Release*, Vol. 42, pp. 29-36 (1996), Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring in vivo in Humans", *Pharm. Res.*, Vol. 12 (12), pp. 1869-1873 (1995), Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", *J. Pharm. Pharmacol.*, Vol. 46, pp. 725-730 (1994), Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electropulsion and Electroosmosis", *Pharm. Res.*, Vol. 12 (11), pp. 1623-1627 (1995).

The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention. Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Additional hair growth stimulants can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of a compound of the present invention. These optional other hair growth stimulants, when present, are typically employed in the compositions herein at a level ranging from about 0.01% to about 15%, preferably from about 0.1% to about 10%, most preferably from about 0.5% to about 5% by weight of the composition.

Vasodilators such as potassium channel agonists including, for example, minoxidil and minoxidil derivatives such as aminexil and such as those described in U.S. Pat. Nos. 3,382,247, 5,756,092, issued May 26, 1998, U.S. Pat. No. 5,772,990, issued Jun. 30, 1998, U.S. Pat. No. 5,760,043, issued Jun. 2, 1998, U.S. Pat. No. 3,289,914, issued Jul. 12, 1994, U.S. Pat. No. 5,466,694, issued Nov. 14, 1995, U.S. Pat. No. 5,438,058, issued Aug. 1, 1995, and U.S. Pat. No. 4,973,474, issued Nov. 27, 1990, (all of which are herein incorporated by reference), and cromakalin and diazoxide can be used as an additional hair growth stimulant in the compositions herein.

One suitable class of additional hair growth stimulant for use herein are antiandrogens. Examples of suitable antiandrogens may include, but are not limited to 5- α -reductase inhibitors such as finasteride and those described in U.S. Pat. No. 5,516,779, issued May 14, 1996 (herein incorporated by reference) and in Nane et al., *Cancer Research* 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5 α -Reductase in vitro and in vivo and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone

acetate, azelaic acid and its derivatives and those compounds described in U.S. Pat. No. 5,480,913, issued Jan. 2, 1996, flutamide, and those described in U.S. Pat. No. 5,411,981, issued May 2, 1995, U.S. Pat. No. 5,565,467, issued Oct. 15, 1996 and U.S. Pat. No. 4,910,226, issued Mar. 20, 1990, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are immunosuppressants or non-immunosuppressants such as 1) cyclosporin and cyclosporin analogs including those described in U.S. Provisional Patent Application No. 60/122,925, Fulmer et al., filed Mar. 5, 1999, herein incorporated by reference, and 2) FK506 analogs such as those described in U.S. Provisional Patent Application No. 60/147,279, Degenhardt et al., filed Aug. 5, 1999; U.S. Provisional Patent Application No. 60/147,313, Degenhardt et al., filed Aug. 5, 1999; U.S. Provisional Patent Application No. 60/147,280, Degenhardt et al., filed Aug. 5, 1999; U.S. Provisional Patent Application No. 60/147,278, Degenhardt et al., filed Aug. 5, 1999; and U.S. Provisional Patent Application No. 60/147,276, Eickhoff et al., filed Aug. 5, 1999; all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are antimicrobials such as selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745 (herein incorporated by reference), clinacyn hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Anti-inflammatories can also be incorporated into the compositions herein as an optional hair growth stimulant. Examples of suitable anti-inflammatories may include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipoxygenase inhibitors such as those described in U.S. Pat. No. 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published Mar. 31, 1994, and FR 2,268,523, published Nov. 21, 1975, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are thyroid hormones and derivatives and analogs thereof. Examples of suitable thyroid hormones for use herein may include triiodothyronine. Examples of thyroid hormone analogs which may be suitable for use herein include those described in U.S. Provisional Patent Application No. 60/136,996, Zhang et al., filed Jun. 1, 1999, U.S. Provisional Patent Application No. 60/137,024, Zhang et al., filed Jun. 1, 1999, U.S. Provisional Patent Application No. 60/137,022, Zhang et al., filed Jun. 1, 1999, U.S. Provisional Patent Application No. 60/137,023, Zhang et al., filed Jun. 1, 1999, U.S. Provisional Patent Application No. 60/137,052, Youngquist et al., filed Jun. 1, 1999, U.S. Provisional Patent Application No. 60/137,063, Youngquist et al., filed Jun. 1, 1999, and U.S. Provisional Patent Application No. 60/136,958, Youngquist et al., filed Jun. 1, 1999.

Prostaglandin agonists or antagonists can also be used as optional hair growth stimulants in the compositions herein. Examples of suitable prostaglandins agonists or antagonists include latanoprost and those described in WO 98/33497, Johnstone, published Aug. 6, 1998, WO 95/11003, Stjerschantz, published Apr. 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Another class of optional hair growth stimulants for use herein are retinoids. Suitable retinoids may include isotretinoin, acitretin, and tazarotene.

Another class of optional hair growth stimulants for use herein are triterpenes such as, for example, those disclosed

in Bradbury et al., U.S. patent application Ser. No. 09/353,408, "Method for Regulating Hair Growth", filed Jul. 15, 1999 and Bradbury et al., U.S. patent application Ser. No. 09/353,409, "Compositions Which Contain Triterpenes for Regulating Hair Growth", filed Jul. 15, 1999, each incorporated by reference in their entirety.

Other classes of optional hair growth stimulants for use herein include flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Pat. No. 5,529,769, JP 10017431, WO 95/35103, U.S. Pat. No. 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Pat. Nos. 5,631,282, 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al., published Sep. 8, 1993 and WO 97/01346 to Bonte et al., published Jan. 16, 1997 (both of which are herein incorporated by reference in their entirety), proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Pat. No. 5,015,470, issued May 14, 1991, U.S. Pat. No. 5,300,284, issued Apr. 5, 1994 and U.S. Pat. No. 5,185,325, issued Feb. 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promoters, analogs or inhibitors such as interleukin1 inhibitors, interleukin-6 inhibitors, interleukin-10 promoters, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interferon agonists and antagonists, hydroxyacids such as those described in U.S. Pat. No. 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin.

Other additional hair growth stimulants are described in detail in, for example, JP 09-157,139 to Tsuji et al., published Jun. 17, 1997; EP 0277455 A1 to Mirabeau, published Aug. 10, 1988; WO 97/05887 to Cabo Soler et al., published Feb. 20, 1997; WO 92/16186 to Bonte et al., published Mar. 13, 1992; JP 62-93215 to Okazaki et al., published Apr. 28, 1987; U.S. Pat. No. 4,987,150 to Kurono et al., issued Jan. 22, 1991; JP 290811 to Ohba et al., published Oct. 15, 1992; JP 05-286,835 to Tanaka et al., published Nov. 2, 1993, FR 2,723,313 to Greff, published Aug. 2, 1994, U.S. Pat. No. 5,015,470 to Gibson, issued May 14, 1991, U.S. Pat. No. 5,559,092, issued Sep. 24, 1996, U.S. Pat. No. 5,536,751, issued Jul. 16, 1996, U.S. Pat. No. 5,714,515, issued Feb. 3, 1998, EPA 0,319,991, published Jun. 14, 1989, EPA 0,357,630, published Oct. 6, 1988, EPA 0,573,253, published Dec. 8, 1993, JP 61-260010, published Nov. 18, 1986, U.S. Pat. No. 5,772,990, issued Jun. 30, 1998, U.S. Pat. No. 5,053,410, issued Oct. 1, 1991, and U.S. Pat. No. 4,761,401, issued Aug. 2, 1988, all of which are herein incorporated by reference.

Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl

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phthalate, decyl oleate, ethyl caproate, ethyl salicylate, iso-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, iso-propyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-m-toluamide, and, 1-dodecylazacycloheptan-2-one.

In all of the foregoing, of course, the compounds of the invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

Composition Examples

The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. In each example, a compound of the present invention other than the one mentioned may be substituted in the example with similar results.

EXAMPLE A

A tablet for oral administration according to the present invention is made, comprising:

Component	Amount
Compound of Example 3	15 mg
Lactose	120 mg
Maize Starch	70 mg
Talc	4 mg
Magnesium Stearate	1 mg

A human female subject weighing 60 kg (132 lbs), suffering from rheumatoid arthritis, is treated by a method of this invention. Specifically, for two years, a regimen of three tablets per day of the above composition is administered orally to the subject.

EXAMPLE B

A composition for topical administration according to the present invention is made, comprising:

Component	Amount
Compound of Example 1	5%
Ethanol	57%
Propylene Glycol	19%
Dimethyl Isosorbide	19%

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topically to the subject.

EXAMPLE C

A composition for topical administration according to the present invention is made according to the method of

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Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: 1. An in vitro Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404-407 (1993), using the compound of Example 2 in lieu of cyclosporin A and using the Novasome 1 for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

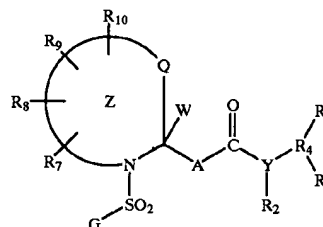
EXAMPLE D

A shampoo according to the present invention is made, comprising:

Component	Ex. C-1	Ex. C-2	Ex. C-3	Ex. C-4
Ammonium Lauryl Sulfate	11.5%	11.5%	9.5%	7.5%
Ammonium Laureth Sulfate	4%	3%	2%	2%
Cocamide MEA	2%	2%	2%	2%
Ethylene Glycol Distearate	2%	2%	2%	2%
Cetyl Alcohol	2%	2%	2%	2%
Stearyl Alcohol	1.2%	1.2%	1.2%	1.2%
Glycerin	1%	1%	1%	1%
Polyquaternium 10	0.5%	0.25%	—	—
Polyquaternium 24	—	—	0.5%	0.25%
Sodium Chloride	0.1%	0.1%	0.1%	0.1%
Sucrose Polyesters of Cottonate Fatty Acid	3%	3%	—	—
Sucrose Polyesters of Behenate Fatty Acid	2%	3%	—	—
Polydimethyl Siloxane	—	—	3%	2%
Cocaminopropyl Betaine	—	1%	3%	3%
Lauryl Dimethyl Amine Oxide	1.5%	1.5%	1.5%	1.5%
Decyl Polyglucose	—	—	1%	1%
DMDM Hydantoin	0.15%	0.15%	0.15%	0.15%
Compound of Example 1	2%	—	—	—
Compound of Example 2	—	5%	—	—
Compound of Example 3	—	—	3%	—
Phenoxyethanol	0.5%	0.5%	0.5%	0.5%
Fragrance	0.5%	0.5%	0.5%	0.5%
Water	q.s.	q.s.	q.s.	q.s.

What is claimed is:

1. A compound having a structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

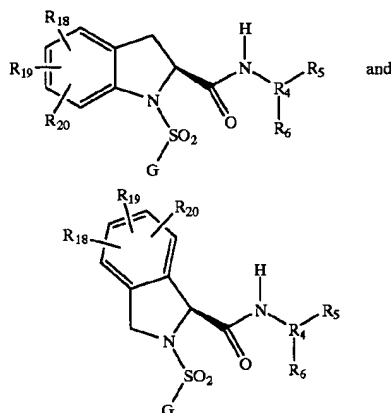
(a) G is selected from the group consisting of alkyl having at least 3 carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl;

(b) Z is a saturated or unsaturated 4-, 5-, 6-, 7-, 8-, or 9-membered heterocycle optionally containing one or more additional heteroatoms selected from the group consisting of O, N, S, S(O), S(O)₂, and P(O)(OK);

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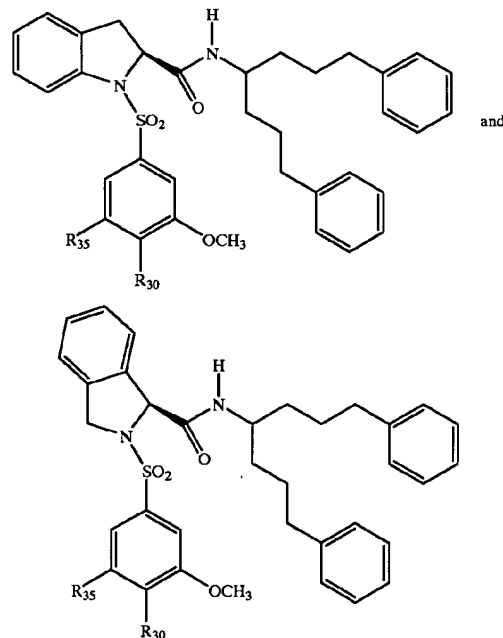
- (c) K is selected from the group consisting of hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl;
- (d) W is selected from the group consisting of nil, hydrogen, and lower alkyl;
- (e) A is selected from the group consisting of nil and alkyl;
- (f) Y is selected from the group consisting of N, O, and S;
- (g) R₂ and R₃ are each, independently, selected from the group consisting of nil, hydrogen, alkyl, and arylalkyl;
- (h) R₄ is selected from the group consisting of methylene and methyne;
- (i) R₅ and R₆ are each, independently, selected from the group consisting of nil, hydrogen, alkyl having at least three carbon atoms, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; or wherein R₅ and R₆ are bonded together to form a carbocyclic or heterocyclic ring; wherein at least one of R₅ or R₆ is not nil or hydrogen;
- (j) Q is selected from the group consisting of CH₂, CHR₉, NR₉, S, S(O), and S(O)₂;
- (k) R₉ and R₁₀ are each, independently, selected from the group consisting of nil, hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, halo, cyano, hydroxy, oxo, imino, —R₁₄SR₁₅, —R₁₄S(O)₂R₁₅, —R₁₄S(O)R₁₅, —R₁₄C(O)R₁₅, —R₁₄C(O)NR₁₅R₁₆, —R₁₄C(O)OR₁₅, —R₁₄OR₁₅, —R₁₄NR₁₅R₁₆, —R₁₄P(O)NR₁₅R₁₆, —R₁₄P(O)OR₁₅R₁₆, and a spiro moiety;
- (l) R₇ and R₈ are bonded together to form an aromatic or saturated, carbocyclic or heterocyclic ring wherein the ring is fused to Z;
- (m) R₁₄ is selected from the group consisting of nil, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl;
- (n) R₁₅ is selected from the group consisting of hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroarylalkyl, arylalkenyl, and heteroarylalkenyl; and
- (o) R₁₆ is selected from the group consisting of hydrogen and alkyl.
2. A compound according to claim 1 wherein Z is a 5-, 6-, or 7-membered heterocycle wherein W is hydrogen.
3. A compound according to claim 2 wherein Z is a 5-membered heterocycle, A is nil, Y is N, and R₂ is hydrogen.
4. A compound according to claim 3 wherein G is substituted phenyl.
5. A compound according to claim 4 wherein R₇ and R₈ are bonded together to form a 5-, 6-, or 7-membered carbocyclic or heterocyclic aromatic ring which is fused to Z.
6. A compound according to claim 5 which is selected from the group consisting of:

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wherein R₁₈, R₁₉, and R₂₀ are each, independently, selected from the group consisting of hydrogen, alkoxy, hydroxy, nitro, amino, alkylamino, cyano, halo, carboxy, thiol, imino, and aryloxy.

7. A compound according to claim 6 which is selected from the group consisting of:



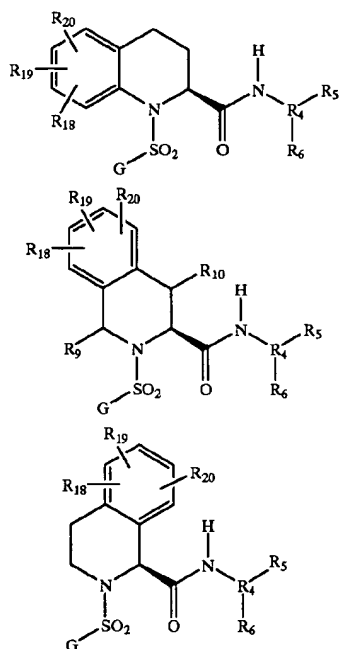
wherein R₃₀ is selected from the group consisting of —OR₃₂ and —OCH₂C(O)OR₃₂, wherein R₃₂ is selected from the group consisting of hydrogen and alkyl, and wherein R₃₅ is selected from the group consisting of hydrogen and —OR₃₆, wherein R₃₆ is selected from the group consisting of hydrogen and alkyl.

8. A compound according to claim 2 wherein Z is a 6-membered heterocycle and wherein A is nil, Y is N, and R₂ is hydrogen.

9. A compound according to claim 8 wherein G is substituted phenyl.

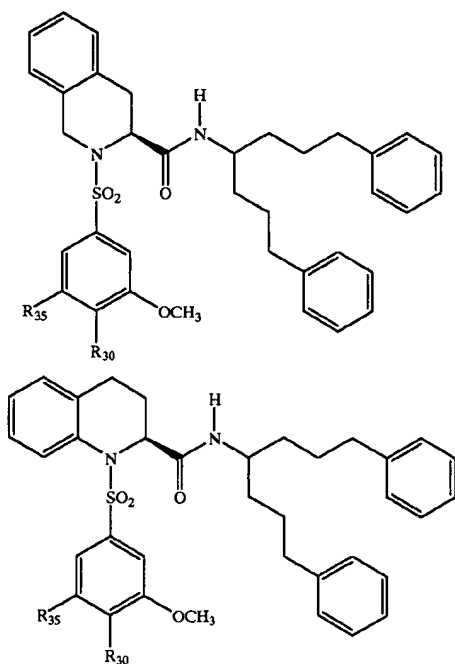
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10. A compound according to claim 9 which is selected from the group consisting of:



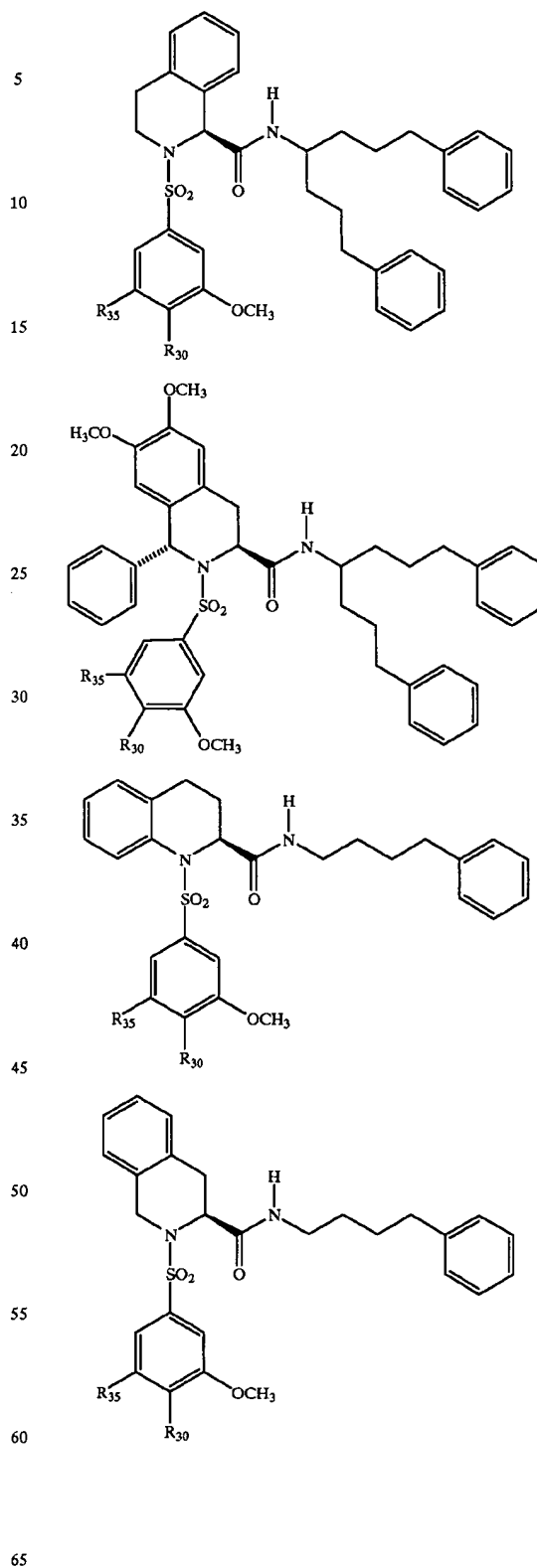
wherein R_{18} , R_{19} , and R_{20} are each, independently, selected from the group consisting of hydrogen, alkoxy, hydroxy, nitro, amino, alkylamino, cyano, halo, carboxy, thiol, imino, and aryloxy.

11. A compound according to claim 10 which is selected from the group consisting of:



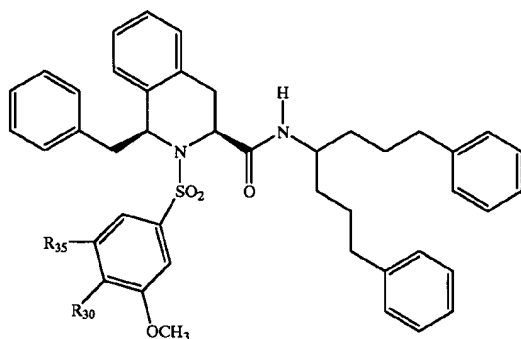
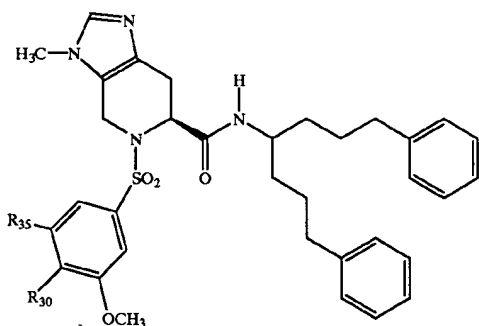
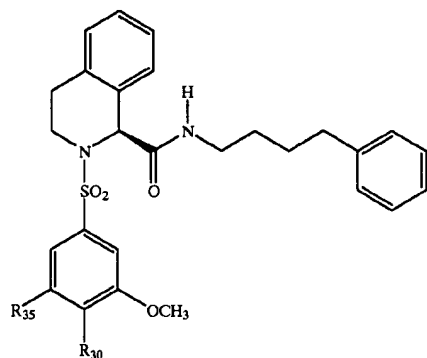
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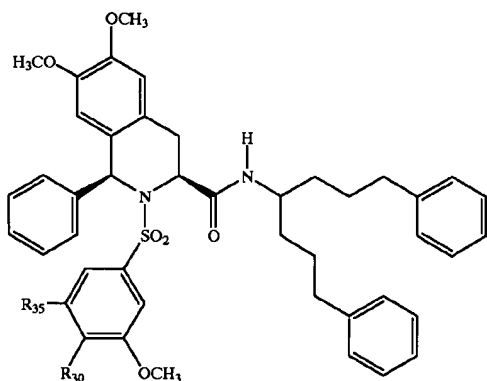


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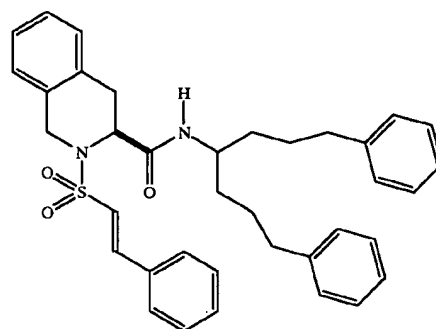
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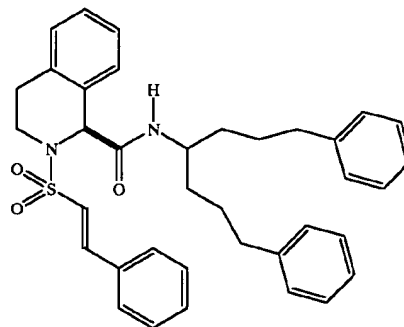
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wherein R_{30} is selected from the group consisting of $-OR_{32}$ and $-OCH_2C(O)OR_{32}$, wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and wherein R_{35} is selected from the group consisting of hydrogen and $-OR_{36}$, wherein R_{36} is selected from the group consisting of hydrogen and alkyl.

12. A compound according to claim 8 which is selected from the group consisting of:



and



13. A composition comprising a compound according to claim 1 and a pharmaceutically-acceptable carrier.

14. A method of treating hair loss comprising administering to a mammal a composition according to claim 13.

15. A method according to claim 14 wherein the administration is topical.

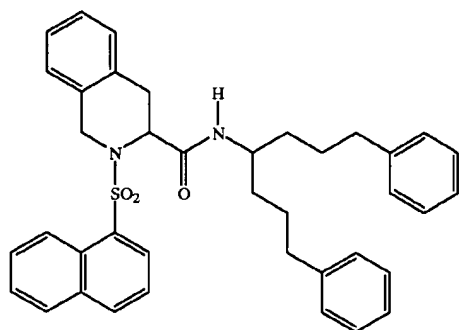
16. A method according to claim 14 wherein the administration is oral.

17. A method of treating or preventing multi-drug resistance comprising administering to a mammal a composition according to claim 13.

18. A composition according to claim 13 additionally comprising a matrix metalloproteinase inhibitor.

19. A compound according to claim 8, wherein the structure is selected from the group consisting of:

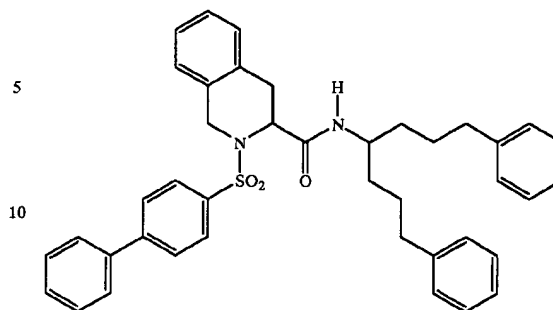
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and

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